VOLUME 101 • MARCH 1958 • NUMBER 3

A.M.A. ARCHIVES OF

INTERNAL MEDICINE

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Norman M. Kaplan and Abraham I. Braude

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S. E. Gould and L. P. Cawley

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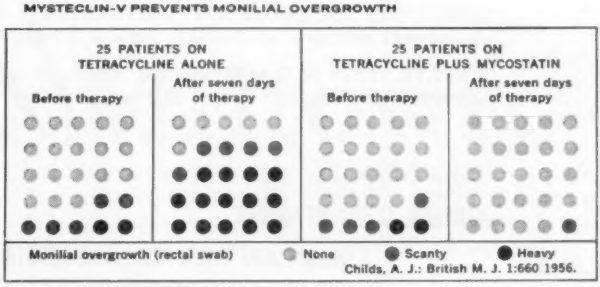

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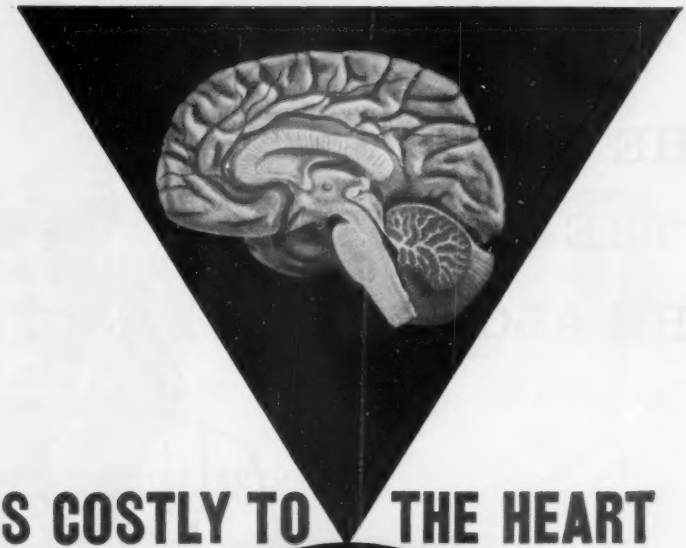

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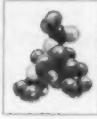

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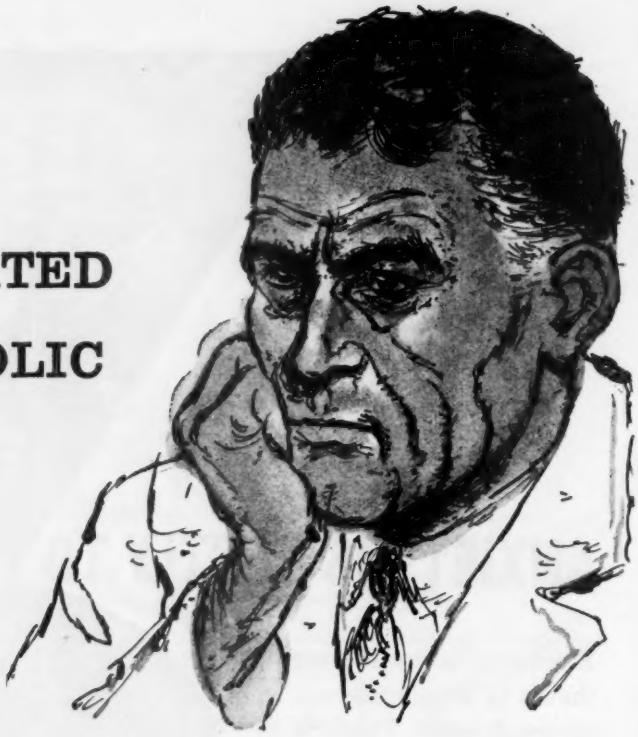

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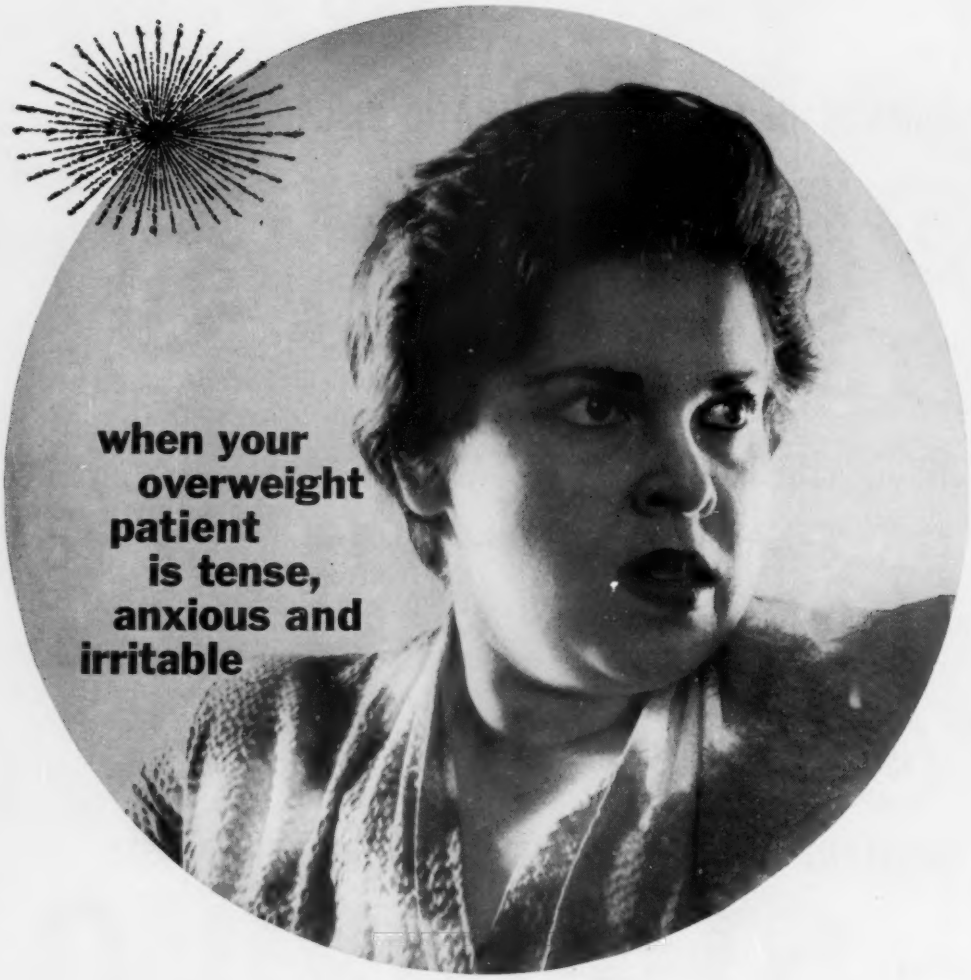

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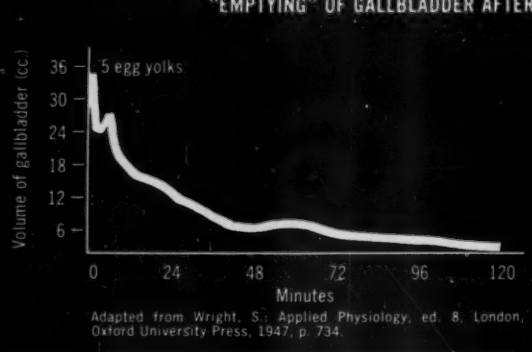

Adapted from Wright, S.: Applied Physiology, ed. 8, London, Oxford University Press, 1947, p. 734.

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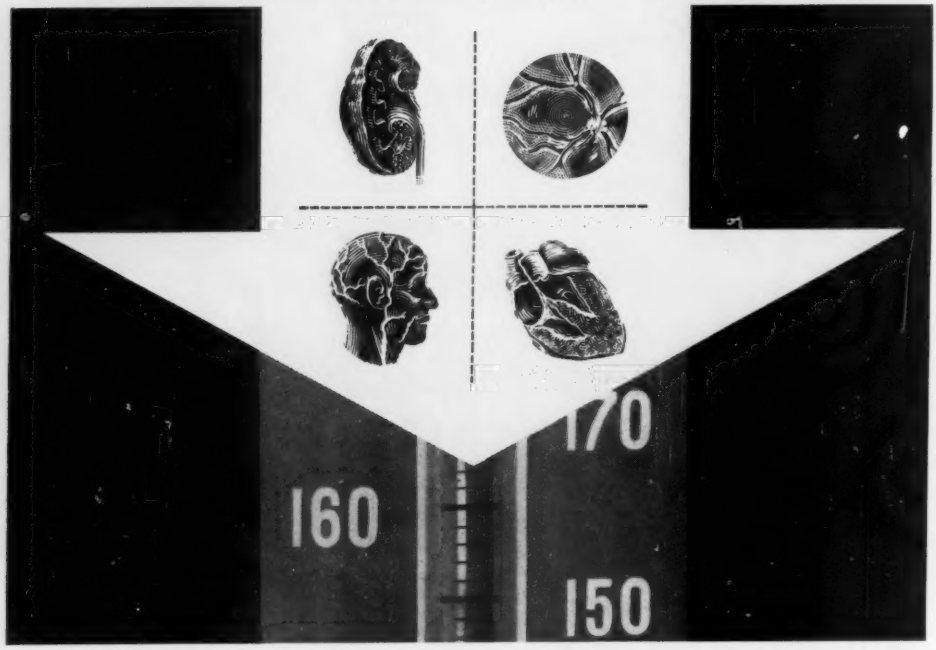

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References: **1.** Moyer, J. H.; Miller, S. I. and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953; **2.** Kuhn, P. H.: Angiology *4*:195 (June) 1953. **3.** Ford, R. V. and Spurr, C. D.: Am. Pract. *5*:251 (April) 1954. **4.** Wolfe, J. B.; Walkow, M. D.; Nagler, J. H. and Anastasia, J.: J. Am. Geriatric Soc. *2*:365 (June) 1954.

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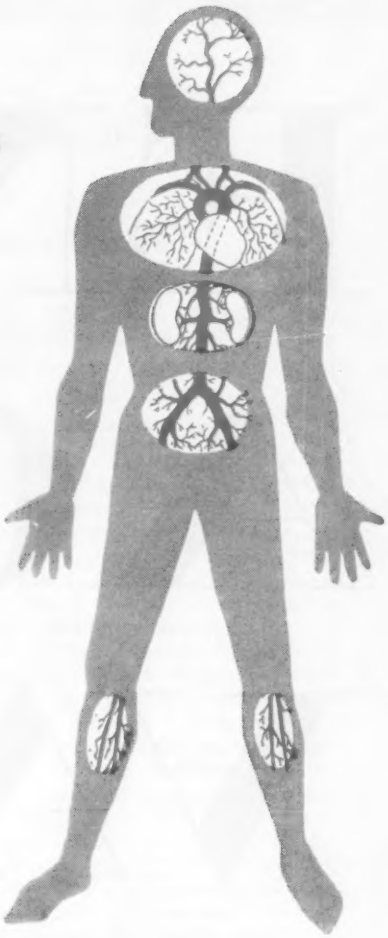

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Hemophilus Influenzae Infection in Adults

Observations on the Immune Disturbance

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The immunity of adults to certain common infections of childhood can usually be related to the acquisition of specific antibody through contact with micro-organisms. Immunity to infection by Hemophilus influenzae, Type B, is an excellent example of the solid and durable resistance acquired against a childhood infection and maintained by repeated exposure to the bacillus. The low rate of adult infection is illustrated by the fact that in 467 cases of H. influenzae meningitis only 15 were in patients over the age of 20.[1-5] An extensive review of the literature has disclosed among adults only 33 cases of meningitis [5-10] and scattered reports of endocarditis, brain abscess, obstructive laryngitis, pyarthrosis,[11] and pneumonia [12] due to H. influenzae, Type B.

While the resistance of most adults to infection by H. influenzae is readily understood on the basis of acquired immunity, little effort has been made to explain the lack of immunity in these rare adults who sustain systemic infections by that organism. Three such patients who were recently admitted to the Parkland Memorial Hospital stimulated an investigation of the immunologic disturbance responsible for their susceptibility to infection by H. influenzae. A description of these cases and experimental observations are presented in this report.

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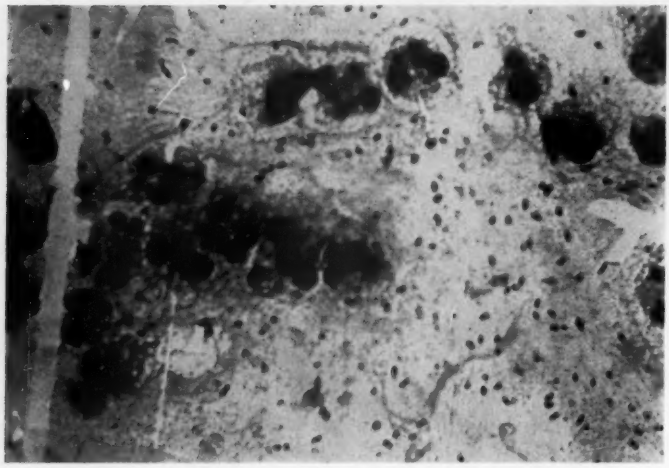
Description of Cases

CASE 1.—A 52-year-old white male itinerant experienced a cough productive of mucopurulent sputum four days before admission (Jan. 17, 1957), while hitch-hiking across Texas in near-freezing weather. This was accompanied by malaise, fever, and pleuritic pain in the right chest anteriorly. Soon after arriving in Dallas, he was found semicomatose and brought to the hospital.

He had been a heavy smoker for 25 years and had had a moderate nonproductive cigarette cough for the last 10 years. Though admitting to heavy alcoholic intake for many years, he denied drinking more than an occasional beer during the past six months. He had been discharged from the Army in 1938 because of "confusion" resulting from syphilis contracted in 1928. The infection was treated approximately two years after the chancre was found. His only other illness had been in 1950, when he was hospitalized for two weeks for "pneumonia." He had apparently recovered completely from this infection after treatment with penicillin.

On admission the patient was confused and slow to respond and appeared acutely ill. A severe cough produced thick mucosanguineous sputum and right anterior pleuritic pain. His temperature was 102 F; pulse, 120; respirations, 24, and blood pressure, 130/70. His pharynx was injected, and there were decreased tactile fremitus, dullness to percussion, diminished breath sounds, many moist rales, and coarse rhonchi over the front and back of the right upper chest. The examination was otherwise negative.

Admission laboratory work revealed Hb., 14.2 gm/100 ml.; WBC, 20,500, with 13 band cells, 81



Smear of sputum from Patient 1. Myriads of Gram-negative bacilli were present, which proved to be H. influenzae, Type B. Gram stain; reduced 38% from mag. × 2500.

polymorphonuclear cells, 6 lymphocytes; urinalysis, negative; normal cerebrospinal fluid; positive Wassermann test for syphilis. A stained smear of the sputum disclosed innumerable encapsulated Gram-negative rods which proved to be H. influenzae, Type B, on culture (Figure). H. influenzae, Type B, was also isolated from two blood cultures.

Treatment was begun with penicillin, 600,000 units q. i. d., and tetracycline, 500 mg. q. i. d., on the basis of a presumptive diagnosis of pneumonia secondary to Bacteroides or Klebsiella pneumoniae. Ten hours later hypotension was noted and the patient was found to be in peripheral vascular collapse. This did not improve after administration of O_2 by mask or intermittent positive pressure but disappeared within 30 minutes after institution of arterenol by continuous intravenous drip (4 mg. in 1000 cc. 5% dextrose and H_2O). This treatment was discontinued after eight hours, and his blood pressure remained at normal levels thereafter.

Upon identification by culture of H. influenzae in sputum and blood, streptomycin, 0.5 gm. b. i. d., and chloramphenicol, 250 mg. q. i. d., were also administered and penicillin was discontinued.

Within 24 hours, the physical findings over the right upper lung changed to those of consolidation. He became afebrile within five days, and slow, progressive resolution took place. Bronchoscopy was negative except for endobronchitis involving the right upper lobe bronchus. All antibiotics were discontinued on the 18th hospital day, and the patient remained asymptomatic thereafter.

CASE 2.—A 40-year-old white woman, a chronic alcoholic with poor dietary intake, gave a history of "pleurisy in the right lung off and on for 20 years," during which time she experienced recurrent "bronchial troubles," with prolonged coughing and expectoration of mucopurulent sputum. Nevertheless, x-rays taken as part of health department requirements for waitresses were always said to have been negative. Though she had begun losing weight for six weeks, she noted no other difficulties until being struck in the right lateral chest during a drunken brawl three weeks before admission. Thereafter, she noted marked right pleuritic pain, soon associated with cough and expectoration of large amounts of thick tenacious pink-tinged sputum and followed by fever, malaise, nausea, and vomiting. These latter symptoms began after a typical alcoholic dabauch five days earlier. On the day of admission, Dec. 16, 1954, physical examination revealed a thin woman appearing both acutely and chronically ill, breathing rapidly, coughing up tenacious reddish brown sputum, and complaining of right lateral pleuritic pain. The temperature was 103 F; pulse, 102; respirations, 30, and B. P., 150/90. The examination was essentially negative except for decreased tactile fremitus, dullness to percussion, and absent breath sounds in the right base, anteriorly and posteriorly. A chest x-ray revealed fluid up to the level of the fifth rib posteriorly. The initial thoracentesis obtained about 400 cc. of cloudy yellowish fluid, with 16,000 WBC and 4000 RBC per cubic millimeter, from which a pure culture of H. influenzae, Type B, was grown. Sputum taken on admission revealed many Gram-negative encapsulated rods, which also proved to be H. influenzae, Type B. Blood cultures were positive for this organism initially as well as on two other occasions during the next two weeks.

Other laboratory results included Hb., 10.6 gm/100 ml.; WBC, 15,600, with a left shift in the

differential count; urinalysis, negative; VDRL test, negative; tuberculin test, negative (1:1000 OT); sulfobromophthalein retention, 17% in 45 minutes; albumin-globulin ratio, 4.0:2.0, and otherwise normal liver function tests. Agglutination tests for Pasteurella tularensis were positive 1:40, and those for Proteus OX19 were 1:20.

Treatment initially consisted of tetracycline, 3 gm. daily, intercostal nerve blocks, parenteral analgesics, constant nebulization with intermittent use of bronchodilators, and repeated thoracenteses. On the fifth day of hospitalization, a segmental rib resection was performed with institution of open drainage of the empyema. An area of cavitation in the right lower lobe was subsequently visualized. Bronchoscopy was negative, as was a subsequent bronchogram. Streptomycin was added during the latter part of her hospitalization. Progressive decrease in the amount of drainage with reduction in the size of the empyema cavity were noted, and follow-up x-rays revealed complete resolution of the pulmonary process. She has subsequently had no respiratory symptoms.

CASE 3.—A 66-year-old white woman was admitted on Oct. 21, 1953, with an 18-hour history of nausea, vomiting, fever, and slight soreness in the neck. A diagnosis of gastroenteritis was made, and she wase treated with parenteral fluids and antispasmodics. However, during the next six hours she became progressively less responsive, and nuchal rigidity became evident. A lumbar puncture revealed grossly purulent cerebrospinal fluid which contained 7200 leukocytes, (99% polymorphonuclear cells). The pressure was only 13 cm. of H_2O, but the sugar content was 20 mg/100 cc. (simultaneous blood sugar, 150 mg.), and the protein, 900 mg. Culture of this fluid and the blood revealed Hemophilus influenzae which was not typable. On admission, Hb. was 14.2 gm/100 ml., and the WBC, 10,400, with a left shift. The urine was cloudy and contained 3+ albumin.

The patient subsequently told that she had fallen and fractured her skull 10 years previously, with drainage of blood through the left ear occurring for six days thereafter. She also admitted to heavy long-standing alcoholic intake but denied recent drunkenness. She had been essentially well before onset of her meningitis, though she had a chronic minimally productive "cigarette cough."

The patient was treated initially with large doses of parenteral penicillin (admission diagnosis being pneumococcal meningitis), with streptomycin being added subsequently. She made a rapid complete recovery and was discharged after a 10-day hospitalization. Further laboratory work revealed a positive blood Wassermann test. Liver-function tests demonstrated sulfobromophthalein retentions of 26% and 12% in 45 minutes; albumin-globulin ratio, 4.7:2.6; alkaline phosphatase, 4.7 Bodansky units; prothrombin time, 65%. Repeat examinations of the spinal fluid showed progressive return toward normal.

The patient has been seen occasionally during the subsequent three years and has remained essentially asymptomatic.

Experimental Observations

Fothergill and Wright[3] correlated the differences in incidence of H. influenzae meningitis with the bactericidal property of blood against this organism. They found the bactericidal titer high in the blood of every person beyond 10 years of age studied. In an earlier study,[13] Ward and Wright showed that this bactericidal mechanism of normal blood is related to the presence of natural antibody and complement and independent of the presence of cellular elements. In addition to these early studies on specific bactericidal antibody, recent investigations have implicated a naturally occurring euglobulin, properdin, in the bactericidal action of blood against many organisms, including H. influenzae.[14] In the light of these facts, the following possibilities were considered before investigating the disturbances responsible for the occurrence of this infection in adults:

1. The absence of naturally acquired specific antibody, resulting from either
   (*a*) Lack of previous contact with the organism or
   (*a*) Disturbances in antibody synthesis (agammaglobulinemia or multiple myeloma)
2. Impairment of natural immune mechanisms other than antibody, and involving
   (*a*) Complement
   (*b*) Properdin
3. Nonspecific environmental conditions, including starvation, fatigue, cold, and alcohol intake.

The first of these (1*a*) would seem to be only a remote possibility in view of the high frequency with which this organism is found in the nasopharynx of normal persons.[15] The absence of γ-globulin has been reported[7] in one instance of H. influenzae meningitis in a 37-year-old woman. Unfortunately, no other determinations of γ-globulin have been described in adult infections with this organism.

The role of complement is well established with respect to its importance in bacterial lysis. However, no evidence for immune disturbances related to its deficiency in humans has been reported. The possibility that a dietary deficiency, especially that of ascorbic acid (vitamin C), may be associated with fall in complement titer has been suggested but not confirmed.[16] The properdin level has been found to be low in a variety of diseases, including the one patient with H. influenzae meningitis studied.[14]

The relationship of adverse nonspecific factors (including starvation, fatigue, and exposure) to the lowering of immunity against infections is considered to be relatively unimportant. Convincing evidence is available, however, that ethanol intoxication lowers native resistance to infection.[17-19]

In an attempt to evaluate these possibilities, a series of experimental observations were made in the patient described in the first case report, in normal adults, and in patients with liver disease in order to uncover the immunologic weakness. The fact that chronic alcoholism was the only evident common denominator among the three adults with systemic H. influenzae infections and the reports of bacteremia due to Gram-negative bacilli in patients with liver disease[20,21] prompted concerted study of the effects of acute and chronic alcoholism on the bactericidal power of blood. In addition, an attempt was made to assess properdin activity against H. influenzae by measuring its susceptibility to the bactericidal action of blood after intravenous administration of typhoid vaccine. This experiment was performed because of the reported fall in serum properdin levels after administration of bacterial lipopolysaccharide and because the tremendous numbers of Gram-negative bacilli in one patient's sputum (Case 1) could have provided a source of such lipopolysaccharide.

Methods and Materials

In all bactericidal tests with H. influenzae, a broth culture of the organism isolated from the blood of the patient described in the first case report was used. It was preserved by storing the growth from an 18-hour culture in Levinthal's broth at —20 C. This was warmed to room temperature before each experiment and subcultured to Levinthal's medium. To insure that the smooth phase existed, capsular swelling was demonstrated with Type B antiserum and iridescence was observed on Levinthal's agar before performance of each experiment.

A strain of Escherichia coli was also used in bactericidal tests; it was isolated from a patient with pyelonephritis and preserved at —20 C in tryptose broth.

Bactericidal activity of the blood from the patient in Case 1 was measured against H. influenzae by Fothergill and Wright's modification of Todd's test[8] and compared with the bactericidal activity of blood from three normal adults and one infant. Serial dilutions of bacteria were made with Levinthal's broth; the inoculated blood or serum was rotated mechanically and then plated with a 3 mm. loop on Levinthal's agar. The plates were examined after 24 and 48 hours' incubation at 37 C. A Gram smear was made on every positive culture to insure that no contamination had occurred. In all experiments the serum was separated by centrifugation of fresh clotted blood, preserved by freezing at —20 C, and allowed to melt by exposure to room temperature before each experiment. A portion of certain sera, as indicated below, was heated for 30 minutes at 56 C for inactivation of complement.

Blood was also obtained from the following subjects, none of whom had received antibiotics for at least six days:

1. Patient T1, described in Case 1, before intravenous injection of 50,000,000 killed Salmonella organisms (typhoid-paratyphoid vaccine, Lederle) and at intervals of one-fourth, one, three, and six hours after injection.

2. Patient T2, being treated with busulfan (Myleran) for chronic myelogenous leukemia, before and after intravenous typhoid vaccine (same dose and time schedule as patient T1.)

3. Subjects 1 and 2, normal young men who were given 200 cc. of Black Label Johnny Walker Scotch Whiskey orally over a one-and-one-half-hour period, on an empty stomach. Blood for alcohol determination and serum to be used for bactericidal tests was obtained 1 hour before, immediately after, and 16 hours after cessation of alcohol intake.

4. Subjects A, B, C, D, all young males, who were admitted to the emergency room for minor

trauma and were acutely intoxicated with ethanol. Blood for alcohol determination was also obtained.

5. Subjects C-1, C-2, C-3, and C-4, all men over age 45, who were admitted to the medical wards with history of chronic alcoholism and found to have Laennec's cirrhosis by physical examination and laboratory procedures.

6. Subject 3, a normal young man, who had never ingested more than 50 cc. of whiskey at one time and had taken none for over one month before.

In testing for the bactericidal property of these sera against H. influenzae, 0.1 cc. of an 18-hour Levinthal's broth culture diluted to a density approximating that of a McFarland No. 1 Standard (300,000,000 organisms per cubic centimeter) was added to 0.5 cc. of serum, and the mixture was shaken by hand. A loopful was plated on agar before incubation, and the mixtures were allowed to stand at 37 C for six hours, during which time they were occasionally agitated by hand. At that time another loopful was plated onto agar. The plates were examined grossly and microscopically for growth over a 48-hour period.

A similar technique was utilized for bactericidal tests with E. coli. Serial dilutions with tryptose broth of an 18-hour culture were diluted to a density approximating that of a McFarland No. 1 Standard, and 0.1 ml. of the 10^{-5} dilution was utilized. This was added to 0.5 cc. of serum; the mixture was agitated briefly, and a zero-hour loopful was plated on E.-M. B. agar. The test tubes were allowed to stand at 37 C, with occasional shaking by hand, and a loopful was plated at 6 and 14 hours. The plates were examined grossly after 24 and 48 hours for growth.

In performance of the intradermal skin test, an 18-hour broth culture of H. influenzae was heated to 65 C for one hour; the suspension was repeatedly washed with saline, and a dilution was made with saline to a density approximating that of a No. 1 McFarland Standard.

Results

1. Investigation of immune mechanisms in an adult recently recovered from an H. influenzae infection.

This patient formed antibodies normally, as evidenced by serologic reactions with streptolysin O, sheep cells, typhoid antigens, and Type B red cells; by dermal reactions to bacterial antigens, and by a normal serum electrophoretic pattern. These results are summarized in Table 1, which indicates that Patients 2 and 3 also formed antibodies normally. Nevertheless, the possibility of an isolated block to the production of antibody against H. influenzae was examined by performance of a bactericidal test with the patient's blood. This patient's blood killed the organism in all dilutions, the highest concentration tested being 2,900,000 organisms in 0.1 ml. of broth. Blood obtained from a 9-month-old infant was bactericidal only up to a concentration of 2900 organisms, whereas the blood of three other adults tested were bactericidal against the highest concentration of H. influenzae B.

The patient's serum was found to kill both H. influenza and E. coli. However, heating the serum to inactivate its complement produced a loss of this bactericidal power.

A hanging-drop preparation of a mixture of H. influenzae broth and the patient's fresh heparinized blood was examined repeatedly over a six-hour peroid. Though the number of organisms diminished pro-

TABLE 1.—*Immunologic Studies in Adults with H. Influenzae B Infections*

Case	Dermal Hypersensitivity	γ-Globulin (Paper Electrophoresis)	Circulating Antibody Titer	Isoagglutinins	Acute-Phase Substances
1	Tuberculin, 0 Histoplasmin, 0 Coccidioidin, 0 E. coli lipopoly saccharide, + H. influenzae, +	Alb. = 3.4 / Glob. 2.0 Electrophoresis Albumin 41% Globulin A_1 = 8% A_2 = 15% β = 15% γ = 21%	Forsmann, 1:7 Typhoid "H," 1:20 Wassermann antigen, + Streptolysin O, 1:125	Anti-B, 1:32	CRP, 1+
2	Tuberculin, 0	•	P. tularensis, 1:40	•	•
3	•	•	Wassermann antigen, +	•	•

• No tests performed.

TABLE 2.—*Effect of Alcohol on Bactericidal Action of Serum*

	Blood Alcohol Level, Mg./100 Cc.	H. Influenzae		E. coli		
		0	6 Hr.	0	6 Hr.	14 Hr.
Normal 1						
Before * (heated at 56C for 30 min.)†	0	+++ ‡	+++	+++	+++	0
Before	0	+++	0	+++	0	0
During	78	+++	0	+++	+	0
After	0	+++	+	+++	+	0
Normal 2						
Before * (heated at 56C for 30 min.)†	0	+++	+++	+++	+++	0
Before	0	+++	0	+++	0	0
During	140	+++	++	+++	0	0
After	0	+++	0	+++	0	0
Normal 3						
Serum	0	+++	0	+++	0	0
Serum & whis.	150	+++	0	§	§	§
Serum & alcohol	150	+++	0	§	§	§
Acute alcoholics						
A	292	+++	+++	++	0	0
B	254	+++	++	++++	++	0
C	277	+++	+++	§	§	§
D	343	+++	++	++	0	0
Cirrhotics (Laennec type)						
C1	0	+++	++	+++	++	0
C2	0	++	0	+++	+++	0
C3	0	+++	+++	+++	0	0
C4	0	+++	0	+++	+	0
Broth control (no serum)		++++	++++	+++	++++	+++

* Serum of normal persons 1 and 2 was taken before, during, and after ingestion of alcohol; that of subject 3 was mixed with alcohol in vitro to give the stated levels.
† Complement inactivated.
‡ + to ++++ indicates relative bacterial growth.
§ Test was not performed.

gressively, no evidence of phagocytosis was observed, despite prolonged close contact between organisms and leukocytes. Moreover, smears of a mixture of organisms and blood allowed to incubate over a six-hour period revealed progressive decrease in the number of organisms but no intracellular bacteria.

In addition to these in vitro experiments, an intradermal skin test with 0.1 ml. of the heat-killed H. influenzae was performed. Though only slight erythema was evident after 6 hours, a 1.5 cm. area of induration with a surrounding 6 cm. area of hyperemia was present after 24 hours.

2. Effect of acute and chronic alcohol intake upon the bactericidal property of serum (Table 2).

Serum taken from three normal young men demonstrated killing of both H. influenzae and E. coli, with loss of this killing after inactivation of complement. The direct addition in vitro of either pure ethanol or whisky in a concentration of 150 mg. of alcohol per 100 cc. of serum did not affect this bactericidal property.

However, serum obtained from the two young men who were given large amounts of whisky to drink had a diminished bactericidal effect against H. influenzae during the time when alcohol was present in the blood in one subject (Subject 2), but not until the next day in the other (Subject 1). Results with E. coli differed in that no loss of bactericidal activity occurred with serum from one subject (Subject 2) while diminution in bactericidal power appeared in the other (Subject 1) both during and after the intake of whisky.

The sera of the four acutely intoxicated men tested had virtually no bactericidal effect in six hours upon the growth of H. influenzae, but only one of the three tested with E. coli allowed its propagation. Tests with the sera of four cirrhotic patients showed variable results, with two killing H. influenzae and three killing E. coli.

3. Effect of typhoid vaccine administration upon the bactericidal property of serum (Table 3).

TABLE 3.—*Effect of Intravenous Typhoid Vaccine on Bactericidal Action of Serum* *

	H. Influenzae		E. Coli		
	0	6 Hr.	0	6 Hr.	14 Hr.
Patient T1					
Before	+++	0	+++	0	0
15 min.	+++	+++	+++	+	0
1 hr.	+++	+++	+++	0	0
3 hr.	+++	+++	+++	0	0
6 hr.	+++	+++	+++	0	0
Patient T2					
Before	++++	0	++	0	0
30 min.	++++	+	++	+	0
1 hr. 30 min.	++++	+	+++	0	0
3 hr.	++++	0	+++	++	0
Control (broth)	+++	+++	+++	++++	+++

* Degree of bacterial growth after exposure to serum is indicated by + to ++++.

Typhoid vaccine was given intravenously to the patient described in the first case report and to a patient with chronic myelogenous leukemia. A striking loss of the bactericidal action against H. influenzae was noted in the serum obtained during the subsequent six-hour interval from the first patient. A much less impressive diminution of bactericidal power was evident in the leukemic blood.

Comment

No explanation of the occurrence of H. influenzae infections has yet been advanced in adults except in the one instance of hypogammaglobulinemia reported by Sanford.[7] While this rare disorder was not present in the alcoholics described in this report, it was possible to demonstrate in other subjects an immune disturbance involving the bactericidal properties of blood and related to the ingestion of alcohol or the development of liver disease.

Earlier studies, by Abbott, have demonstrated that the daily administration of intoxicating amounts of alcohol lowered the native resistance of rabbits to infection by Streptococcus pyogenes and, to less degree, by E. coli.[17] Others [18,19] have shown a reduction in resistance to pneumococci in rabbits given intoxicating amounts of alcohol. This loss of immunity to pneumococci was thought to be related to an inhibition of the normal vascular inflammatory responses, so that leukocytes did not mobilize at the site of infection. Such a disorder would be of little importance in H. influenzae infections, however, in view of our studies, as well as those of Ward and Wright,[13] which have demonstrated that the bactericidal action of normal blood against H. influenzae depends wholly on the antibody-complement mechanism, without any apparent phagocytic component.

The possibility that alcohol destroys antibody seems to have been excluded by the observation that alcoholic intoxication does not hinder existing antibody production.[18,22] However, a marked decrease in the production of "immune substances" was reported by Friedberger in rabbits given injections of a culture of Vibrio cholerae and then given alcohol over long periods of time.[23]

A more reasonable possibility is that there are reductions in the level of complement, known to be necessary for in vitro bactericidal action against H. influenzae.[13] Abbott and Bergey, in 1903, reported that the serum of rabbits given less than 150 cc. of absolute alcohol over a 25-day period had less power for reactivating heated hemolytic immune serum than did the serum of normal rabbits. When alcohol was fed to rabbits in amounts of 5 to 10 cc. daily for three days, a marked fall in the complement titer was noted.[25] Yet these investigators and others [26,27] have shown an increase in the level of complement in the serum of animals given larger doses of alcohol over a longer period of time.

While no studies have been reported on the effects of alcohol on properdin, a nonspecific bactericidal substance in human blood, it has been shown that properdin levels are affected by bacterial lipopolysaccharides.[27] The injection of small amounts of these materials produced a marked rise in the serum properdin level, whereas larger doses are attended by a considerable fall in the properdin titer, with coincident fall in resistance to infection.[27,28] The increased immunity to infection evoked in mice by bacterial lipopolysaccharides appeared to be effective only against infections produced

by endotoxin-bearing organisms, which were found to be highly susceptible to the bactericidal action of the properdin system.[27] Pillimer has suggested that a fall in properdin titer may accompany liberation of large amounts of bacterial products,[29] which could conceivably occur in overwhelming infections by Gram-negative organisms.

The results of the experiments reported in this study give support to the previous demonstrations in animals of a loss of native resistance to infection under the influence of alcohol. In both acute and chronic alcoholism in man, bactericidal properties were diminished against both H. influenzae and E. coli. That this alteration is due to a change in complement titer can only be inferred, as no attempt has been made to isolate the exact immunologic defect. Similarly, the importance of properdin can only be suspected from the observation that the injection of Gram-negative bacilli, a maneuver shown to alter serum properdin levels, has been found to decrease the bactericidal property of serum against these two organisms.

The evidence obtained from these limited studies, as well as that gleaned from the literature, suggests that the bactericidal property of the patient's blood may fall temporarily under various adverse circumstances, including acute and chronic alcoholism. This diminution of acquired immunity might permit the implantation and spread of Gram-negative bacilli, particularly those normally residing in the oropharynx and likely to be aspirated during periods of central nervous system depression. As the Gram-negative bacilli proliferate and burst into the circulation it is conceivable that a second fall in immunity may be caused by lowering of serum properdin levels. These two mechanisms may well explain the occurrence of systemic infections against which adults normally have adequate protection.

Conclusions and Summary

The rarity of Hemophilus influenzae infections in adults has been long recognized, but an explanation for their occurrence has not been offered.

Three cases of H. influenzae infections in adults seen during the past five years are reported. A detailed investigation of the immunologic properties of one of these patients revealed no disturbances in antibody formation.

Acute and chronic alcoholism has previously been shown to lower native resistance to infection in animals. Application of bactericidal tests has revealed, for the first time, a similar decrease in immunity in humans under the influence of alcohol.

A mechanism known to lower serum properdin levels has also been found to decrease serum bactericidal properties for H. influenzae and Escherichia coli in one of the patients.

A correlation has been made between these experimental observations and the occurrence of infections to which adults are usually immune.

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Unsuspected Healed Myocardial Infarction in Patients Dying in a General Hospital

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How common is clinically unsuspected healed myocardial infarction among patients in a general hospital? In order to answer this question, we reviewed a series of 5000 consecutive autopsies from 1945 to 1955, inclusive, at this 500-bed general hospital. This is the county hospital of Wayne County, in which the city of Detroit is located. In addition to the general hospital division, the institution has a psychiatric division with about 3500 mental patients and an infirmary with about 2500 indigent inmates (about 2030 men and 470 women).

After selecting the autopsy protocols of cases with old myocardial infarcts, the corresponding clinical charts were reviewed, with particular reference to evidence of cardiac or vascular disease. All cases were excluded in which the clinical history or electrocardiographic, radiologic, or physical findings led to a diagnosis or to suspicion of myocardial infarction, whether old, recent, or fresh. A systolic blood pressure of 160 mm. or over or a diastolic blood pressure of 100 mm. or over was regarded as evidence of hypertension.

The autopsy protocols were reviewed, with particular reference to cerebral infarcts; disease of the coronary arteries; presence and location of old, recent, or fresh myocardial infarcts; ventricular aneurysm, and weight of the heart. Old infarcts were grossly white or gray-white and microscopically were composed of fibrous or dense scare tissue. Localized isolated areas of fibrosis 0.5 cm. or less in diameter were arbitrarily excluded. The heart of a man was regarded as hypertrophied if it weighed 400 gm. or more, and that of a woman, if it weighed 350 gm. or more.

Findings

1. *Myocardial Infarcts.*—As may be seen in the Table, myocardial infarcts (one or more) were found in 588 autopsies (11.76%). In 136 autopsies (2.7%) the infarct was fresh or recent, and in 452 (9.04%), old. Of the 452 hearts with old infarcts, in 277 (5.54%) old, recent, or fresh infarction was diagnosed or suspected. In 175 autopsies (3.5%) one or more old myocardial infarcts were found which were not clinically diagnosed or suspected.

Of the 175 hearts with old healed unsuspected infarcts, in 120 the infarct was located anteroseptally or laterally in the left

Incidence of Myocardial Infarction Among 5000 Consecutive Autopsies, According to Type of Infarct (Fresh or Recent, Old Diagnosed or Suspected, or Old Unsuspected), Race, and Sex

Group of Patients	Type of Infarct	Patients, No.	Patients with Infarcts	
			No.	%
All patients		5,000	588	11.76
	Fresh or recent		136	2.72
	Old, diagnosed, or suspected		277	5.54
	Old, unsuspected		175	3.5
White		4,212	541	12.8
Male		3,045	399	13.0
Female		1,167	142	12.2
Negro		788	47	6.0
Male		507	33	6.5
Female		281	14	5.0
All males		3,552	432	12.2
All females		1,448	156	10.8

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ventricle; in 48, posterobasally; in 6, at the apex and base, and 1, in the right atrium. In addition, in 11 hearts with old apical infarcts there was associated recent or fresh infarction, and 1 heart with old infarcts both at the apex and base had a fresh apical infarct. Aneurysms were noted in eight infarcts, seven of which were apical.

2. *Race, Age, and Sex of Patients.*—Based upon the total number of persons in each group that came to autopsy, the incidence of infarcts among white patients (12.8%) was more than twice as great as that among Negro patients (6.0%). The ratio of white patients to Negro patients with infarcts was 2.13:1. Relatively more men than women were found to have infarcts (12.2% of all men, compared to 10.8% of all women), the ratio being 1.13:1. This disproportion between the sexes was slight for white patients (13.0% of men, compared to 12.2% of women) but greater for Negroes (6.5% of men, compared to 5.0% of women).

The average age of all 588 patients with infarcts was 68.2 years. The average age of all Negro patients with infarcts was 61.8 years; the average age of those with fresh infarcts, 58.1 years, and of those with old suspected infarcts, 54.2 years. For every type of infarct, the average age of Negro women was less than that of Negro men.

During 1950 (the median year of the period covered in this study), 67% of the 7202 patients admitted to the general hospital were men; the average age of the patients was 51.14 years, and the average age of those who came to autopsy was 64.3 years.

The following data refer to the 175 patients with old unsuspected infarcts.

Old healed unsuspected infarcts were found in 127 men (3.6% of all autopsies of men) and in 48 women (3.3% of all autopsies of women). The average age of the 175 patients was 71.0 years; the average age of the men, 70.6 years (white men, 70.7; Negro men, 70.2), and of the women, 72.2 years (white women, 72.4; Negro women, 69.0). One patient was under 50 years (age 49); 23 were aged 50-59 years; 57 were aged 60-69 years; 53 were aged 70-79 years, and 41 were aged 80 years or over. Thus, only 13.7% of patients with old "silent" infarcts were less than 60 years old, and 53.7% were aged 70 or over.

3. *Heart Failure.*—Hypertension was found among 47% of patients who had heart failure, compared to 32% among those who did not have heart failure. Cardiac hypertrophy, however, was found in 71% of those who had heart failure, compared to 40% of those who did not have heart failure.

4. *Cerebral Thrombosis.*—Physical findings of hemiplegia were noted in 45 cases, and in 7 additional cases cerebral thrombosis or infarction was found at autopsy. In 26 patients the principal lesion was cerebral thrombosis.

5. *Diabetes Mellitus and Gangrene.*—Twelve patients had a history of diabetes, and of these four had gangrene of the feet. In addition, arteriosclerotic gangrene of the feet was recorded in eight nondiabetic patients. In five patients gangrene was the principal lesion at autopsy.

6. *Electrocardiographic Findings.*—No electrocardiogram was made in 119 patients. Among the remaining 56 patients, the electrocardiogram was essentially normal in 23 and abnormal in 33. Evidence of left bundle-branch block was noted in seven; in these patients one could not rule out old myocardial infarction.

7. *Principal Causes of Death.*—In a majority of cases, the presenting complaint or predominant physical findings pointed to some major noncardiac condition. The principal causes of death were judged to be pulmonary disease in 47 (embolism or infarction in 5), cardiac disease in 39 (congestive failure in 29; fresh infarction in 5), neoplastic disease in 34, vascular disease (of brain, or gangrene of foot) in 31, and miscellaneous lesions in 24 (perforated peptic ulcer in 6). Of 29 patients with congestive failure, electrocardiograms were taken in 12 patients; 4 of these were normal,

and 8, abnormal but not diagnostic of infarction.

Comment

Barnes and Ball,[1] of the Mayo Clinic, found myocardial infarcts in 4.9% of a series of 1000 consecutive autopsies performed prior to 1931. McCain and his associates,[2] at Western Reserve University, found an incidence of 7.8% infarcts among 3559 autopsies performed during the years 1936 through 1945. The average age of their patients at death was 61.5 years (men, 60.9 years; women, 62.9 years; white patients, 62.2 years; Negro patients, 56.1 years). They encountered myocardial infarcts in 8.69% of men autopsied and in 6.47% of women autopsied, giving a ratio of men to women with infarcts of 1.32:1. The corrected ratio of white to Negro patients with infarcts was about 2:1; in our material this ratio was 2.13:1.

Of the 5000 autopsies, 841 were performed on psychiatric patients. The incidence of infarcts among psychiatric patients autopsied (12.1%) was approximately the same as that among nonpsychiatric patients (11.7%), so that this group of patients did not unduly affect the incidence of 11.76% of myocardial infarcts found among all patients.

Significant are the lower frequency of infarcts (less than half) among Negroes compared to white persons and the lower average age of Negroes, particularly of Negro women.

It is astonishing that the incidence of old healed "silent" infarcts should be as high as 3.5% of all autopsies. This represents 30% of all infarcted hearts encountered at autopsy. This finding indicates that a myocardial infarct is often well tolerated by the patient. Since the average age of the 175 patients with old unsuspected infarcts was 71 years, it is evident that these patients may live out their expected life span.

In this connection it is interesting to note that Weinberg,[3] of the Medical Examiner's Office of New York City, found old myocardial infarcts in 32% of persons who died suddenly and unexpectedly from any type of coronary artery disease. Spain[4] encountered in the material of the medical examiner's office of Westchester County, New York (a well-to-do residential community close to New York City), old healed myocardial infarcts among 25% of persons who died suddenly without having had previous medical attention and who, for the most part, were unaware of having had coronary artery disease.

Patients with chronic heart failure, regardless of their previous level of blood pressure, may be expected to develop cardiac hypertrophy as a compensatory measure. This is borne out by the finding of cardiac hypertrophy in 71% of patients with old healed "silent" infarcts who had heart failure, compared to only 40% of those without failure. The blood pressure was elevated in 47% of the former group of patients and in 32% of the latter group.

Patients 50 years or over who enter the hospital with symptoms or signs that do not point directly to disease of the heart may have had angina, precordial distress, or heart failure and may forget, neglect, or be unable to give this information at the time of their last admission. The examining physician, centering his attention on the presenting complaints or findings, may well overlook the possibility that the patient has a healed myocardial infarct. In these patients one should nevertheless look for evidence of an old myocardial infarct if any one or more of the following conditions exist: hypertension, history or findings of cerebral thrombosis or hemorrhage, senility, urinary or fecal incontinence, diabetes mellitus, arteriosclerotic gangrene of feet, vascular lesions of eyegrounds, or hypothyroidism.

Perhaps a careful electrocardiographic examination with multiple unipolar chest leads would have detected the myocardial infarct in most of the 119 patients who had no tracing, of those who had a negative

tracing, and of those with an abnormal tracing which was not diagnostic of myocardial infarction. In the last group of patients, only one or a limited number of leads was taken.

Summary

In order to determine the incidence of old healed unsuspected myocardial infarcts among patients dying in a county hospital, we reviewed the protocols of 5000 consecutive autopsies from 1945 to 1955, inclusive, and the clinical records of all patients who were found to have infarcts at autopsy. The total number of hearts with infarcts, whether old, recent, or fresh, was 588 (11.76%). The ratio of men to women with infarcts, among those who came to autopsy, was 1.13:1; of white to Negro patients, 2.13:1.

Healed unsuspected (old, "silent") infarcts were found in 175 patients (3.5%) of all who came to autopsy, and constituted 30% of all myocardial infarcts encountered at autopsy.

The majority of the 175 patients with unsuspected healed infarcts (53.7%) were 70 years or older, and only 1 was less than 50 years old. Those who had congestive heart failure had associated hypertension, and particularly cardiac hypertrophy, more often than patients who did not have congestive failure.

Electrocardiograms were taken in only 56 of the 175 patients with old unsuspected infarcts. In 33 the tracing was abnormal but not diagnostic of infarction. It is believed that multiple unipolar chest leads would have revealed evidence of infarction in many of these 175 patients.

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The Effect of Therapeutic Mobilization on Hypercalciuria Following Acute Poliomyelitis

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Hypercalciuria and extensive osseous demineralization predictably follow illnesses in which there is either flaccid or spastic muscle paralysis. In poliomyelitis, in particular, previous work in this laboratory [1] has demonstrated that there are two aspects in the mineral loss. During approximately the first three to eight weeks after the onset of illness, urinary calcium values rise to about twice the normal maximum of excretion. This rise is as marked in mildly paralyzed subjects as it is in patients suffering extensive muscle denervation; thus there is no direct quantitative relationship between the extent of paralysis and the degree of daily hypercalciuria in this early phase. During the period of from 2 to 12 months after the onset of poliomyelitis, however, the duration of hypercalciuria is directly related to the extent of paralysis. Excessive calcium loss may last as long as 40 weeks in patients with motor paraplegia, while quadriplegic subjects continue to lose abnormal amounts of urinary calcium for 12 months or more. The prolonged wastage of calcium salts not only creates a profound depletion of body mineral stores but also perpetuates the danger of renal and bladder calculus formation.

The loss of stress and strain on bones which results from immobilization has been invoked as the major factor responsible for inducing and maintaining postparalytic osteoporosis and hypercalciuria.[2] Conversely, mobilization has often been credited as being effective in reducing or reversing the hypercalciuria. There have been few quantitative studies of remobilization in paralyzed persons to support this latter inference, however. The normal physiological mobility provided by return of nerve and muscle function is impossible to attain in the severely paralyzed patient. The present study was designed, therefore, to determine whether any artificial mobilizing procedures could ameliorate or reverse the intensity or duration of hypercalciuria among severely paralyzed subjects.

Plan, Materials and Methods

The effects of rocking, vigorous physical therapy, sitting, standing, and crutch-walking on hypercalciuria were studied in both adolescent and adult patients severely paralyzed by poliomyelitis. Calcium excretion patterns were analyzed to determine whether therapeutic mobilization immediately reduced the intensity of hypercalciuria below control periods. In addition, the duration of hypercalciuria in subjects mobilized early was compared with the duration of hypercalciuria in comparably paralyzed patients for whom mobilization had been delayed.

Subjects were grouped together according to the extent of their paralysis and studied at the Northwest Respirator and Rehabilitation Center for periods ranging from 4 to 10 months. Sixteen quadriplegic patients and twenty-one patients with motor paraplegia or moderately extensive scattered paralysis were selected to determine the metabolic effects of mobilization. No patient had clinical or radiographic evidence of renal or bladder calculi during the period of observation. Within each clinical group, the subjects had similar degrees of paralysis but differed in the types of mobilization they received and the time

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after onset of the illness when these procedures were instituted. In general, subjects mobilized early after the onset of poliomyelitis were those cared for in the Center from earliest convalescence. Subjects mobilized late usually had been in other hospitals for weeks or months after the onset of poliomyelitis. During this time their physical treatment had been limited to in-bed physical therapy. A few of the subjects mobilized late had been too ill with medical complications of poliomyelitis early in convalescence to permit any strenuous therapy.

All patients were maintained with a modified balance study for calcium. Dietary calcium was calculated at either 0.5 gm. or 0.8 gm. daily, with use of standard tables. Twenty-four-hour urine collections were made on Monday through Thursday of each week, and quantitative aliquots were pooled for weekly analysis of calcium and phosphorus by standard methods.[3,4] The constancy of creatinine excretion[5] was used to check the accuracy of urine collections. Stools were collected in weekly pools, were homogenized, and were wet-ashed, and an aliquot was analyzed for calcium.

Mobilizing procedures were initiated at the beginning of a week; these procedures then continued for a specified number of weeks or indefinitely. Passive and active exercises in bed were provided as part of the routine care for all patients from the time they were first treated. Since control studies were lacking, the effect on calcium excretion of these limited manipulations could not be ascertained.

Controlled mobilizing procedures were as follows.

1. *Rocking Bed.*—This consisted of removing a patient from the inertness of being in a body respirator or hospital bed to the constant motion of a rapid-rocking bed. The duration of rocking each day varied according to respiratory need but usually was 12 to 20 hours.

2. *Tank Treatment.*—This marked the onset of vigorous physical therapy, including underwater therapy. The duration of such activity was approximately two and one-half to four hours daily.

3. *Sitting.*—This designated wheel-chair sitting at an angle greater than 45 degrees from the horizontal. Sitting at this height was maintained for from three to eight hours daily.

4. *Standing.*—Subjects were stood on a tilt table at 85 degrees from the horizontal for a minimum of from one-half to one hour daily.

5. *Crutch-Walking.*—This designated ambulation with the lower extremities supported by braces and the use of crutches for support and propulsion. The activity occupied one to two hours daily up to the point where independence of crutches was achieved.

6. *Walking.*—This designated ambulation in which canes or braces provided only a steadying role.

Results

The effects of passive mobilization were analyzed by grouping the patient material according to the extent of paralysis.

Quadriplegia.—Sixteen subjects who were paralyzed extensively in the trunk and all four extremities were studied for an average duration of 27 weeks each. There were seven males and nine females. Most patients had recovered only minimal function in the arms and hands, and the ability to move voluntarily was extremely limited in all. All of these subjects had been treated in respirators during their acute illness, and during convalescence only two were completely freed of artificial respiration.

Hypercalciuria persisted for an average of 11 to 12 months after onset of poliomyelitis.[1] All subjects received passive and limited active physical therapy; all but one were treated on the rocking bed; all sat erect in wheel chairs; most received underwater therapy, and many stood on the tilt table. None of these mobilizing measures favorably influenced the steady demineralization which the quadriplegic patient suffered.

Among both sexes there were subjects who rocked, sat, stood, and received tank therapy relatively soon after the onset of poliomyelitis. By contrast, among both sexes there were subjects who were kept in body respirators for months and for whom some of the mobilizing activities were started either late or not at all. Figure 1 graphs the weekly urinary calcium excretion levels in six males and five females. Their calcium excretion showed no significant decline subsequent to mobilizing activities. No significant difference in the intensity of hypercalciuria late after poliomyelitis was observed between those patients who were mobilized early and those for whom mobilization was delayed.

Weekly variations of greater than 100 mg. per day in calcium excretion were

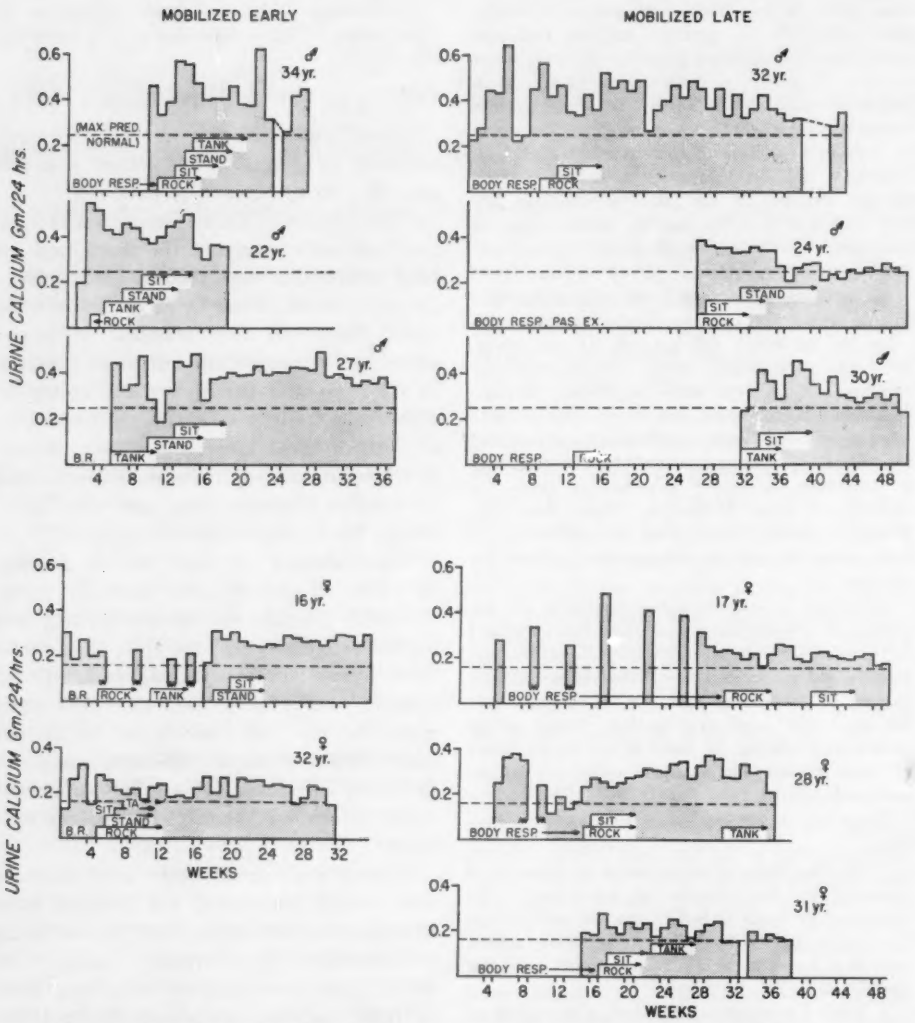

Fig. 1.—The effect of mobilization on hypercalciuria in quadriplegic patients. The patients on the left hand side were mobilized relatively early, and all were subjected to standing. The patients whose excretion is graphed on the right side were mobilized later on in the course of illness, and often standing was omitted from their therapy. No difference in duration and degree of hypercalciuria was noted between the two groups for each sex. The maximal normal calcium excretion was considered to be 250 mg. per 24 hours for males and 160 mg. per 24 hours for females.[1]

observed in several subjects. This variability in mineral excretion sometimes was associated with symptomatic physiological manifestations of greater emotional lability than was seen in other subjects. Several subjects showed sharp increases in calcium excretion of 100 to 300 mg. per 24 hours during the week following the institution of new therapeutic procedures. This response occurred particularly during the first three months after onset of poliomyelitis or when patients were unusually apprehensive about undertaking a new activity. Corticotropin (ACTH) administration was followed by increased calcium excretion in one of the labile subjects (Fig. 2). No change in

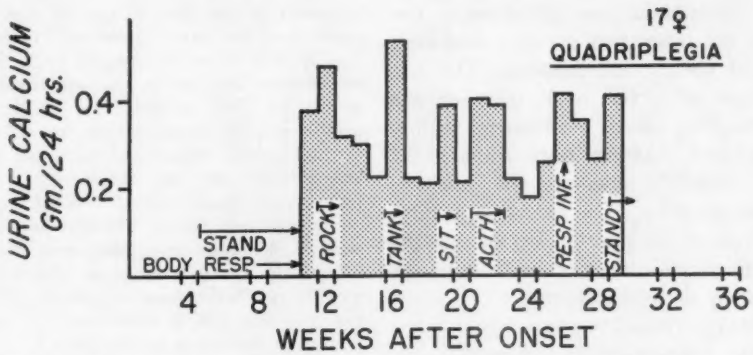

Fig. 2.—Lability in calcium excretion associated with mobilization and corticotropin administration. There was a marked increase over the elevated base line of calcium excretion whenever a new physical treatment was introduced in this young woman. Corticotropin administration as well as a respiratory infection were followed by a similar response.

calcium excretion followed the use of this hormone in two other subjects whose excretion patterns previously had remained more stable during mobilizing procedures. Suitable subjects have not recently been available to extend these limited observations because of the decline in attack rate of poliomyelitis.

Paraplegia and Moderate Scattered Paralysis.—Twenty patients with hypercalciuria in these two groups were studied within the first eight months after onset of poliomyelitis. Observations were made on 15 subjects for 4 to 24 weeks after instituting tank therapy, sitting and standing. There was no significant reduction in urinary calcium excretion following any of these procedures. Four subjects provided suitable material to analyze the value of walking in ameliorating hypercalciuria; Figure 3 graphs their calcium excretion patterns. The extent of paralysis was comparable except for the patient represented in the lower left graph, who had significantly less denervation in his lower extremities than did the other three. Walking was initiated in the patients represented in the left-hand graphs as soon as the muscular capacity for this act re-

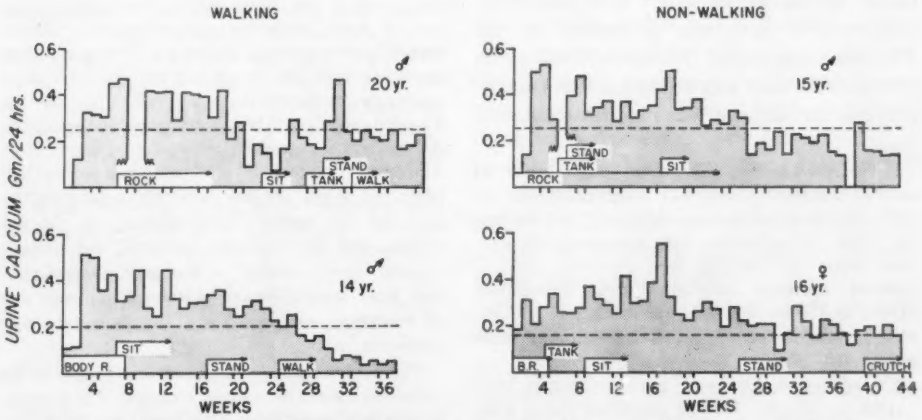

Fig. 3.—The effect of walking on hypercalciuria. Note that in the two upper graphs weekly calcium excretion falls below the predicted maximum several weeks before walking actually begins. Only the patient represented in the lower left graph, who had much less lower-extremity paralysis than did the other patients, showed a progressive decline in calcium output after ambulation.

turned. Ambulation was intentionally delayed in the other two patients, however, because of obesity and scoliosis. The calcium excretion curves in all four subjects were roughly similar, although sitting, standing, and walking were initiated at markedly different intervals after the onset of poliomyelitis. The extent of paralysis appeared to be more important that the specific therapeutic activity in determining the duration of hypercalciuria.

"Pseudohyperparathyroidism."—After paralysis or fracture, some adolescents develop complex metabolic changes, including osteoporosis, hypercalciuria, hypercalcemia, hypophosphatemia, and renal damage with hyposthenuria. Albright and his co-workers termed this syndrome "pseudohyperparathyroidism."[6] Subsequently the same syndrome was recognized in young adults with poliomyelitis.[7] Hypertension and encephalopathy with delirium and convulsions have been described accompanying the above metabolic changes, particularly in association with azotemia and hypercalcemia. Both Albright and subsequent workers[6,8,9] concluded that pseudohyperparathyroidism is a complication of immobilization and advised rapid remobilization to treat this complex of symptoms and metabolic deficiencies. An opportunity to study the effect of therapeutic ambulation on a boy with pseudohyperparathyroidism was presented to us. The following report details the findings on this patient, who was studied while a modified calcium balance was maintained for 18 weeks.

A 16-year-old boy contracted poliomyelitis in another community and was hospitalized Oct. 6, 1954. He required a respirator until mid-December, 1954. Hypertension, with average blood pressure levels of 140/110, was observed, and he suffered recurrent headaches with intermittent nausea and vomiting. He was transferred to the Northwest Respirator and Rehabilitation Center on Jan. 10, 1955.

On admission, his blood pressure ranged from 130/80 to 140/100. He had prominent facial acne, was emotionally labile, and complained intermittently of nausea. His vital capacity was 2.3 liters (50% of predicted). He had moderate weakness in the shoulder girdles, excellent strength in the remainder of his upper extremities, and complete paralysis of his lower extremities. His hematocrit was 35. His urine contained 10 to 20 WBC and no albumin and had a relatively fixed specific gravity of 1.005 to 1.010. The BUN was 25.5 mg/100 cc.; the serum calcium was 17.1 mg/100 cc.; the serum sodium and potassium were 135 and 3.5 mEq. per liter, respectively. The serum phosphorus ranged from 2.5 to 3.1 mg/100 cc. during the study period. The alkaline phosphatase was 5.4 Shinowara units; the serum albumin was 3.7 gm/100 cc., and the serum globulin was 3.3 gm/100 cc. The phenosulfonphthalein (PSP) dye excretion was 35% in two hours. An intravenous pyelogram was within normal limits.

A calcium balance study with the calcium intake strictly calculated at 0.5 gm. was started on the 17th week after the onset of poliomyelitis; Figure 4 illustrates the study period. Passive standing, 60 minutes daily, was begun on the 19th week. His strength in the shoulder girdles improved markedly, and he started crutch-walking with long leg braces during the 21st week. There was no return of muscle function in the lower extremities, however. By the 25th week he was spending at least two hours daily ambulating with crutches and progressively improved in this function. The serum calcium gradually declined to 15 mg/100 cc. by the 26th week, and nausea and vomiting also gradually disappeared during this period.

Hypercalciuria continued to average over 600 mg. per day, despite ambulation and restriction of calcium intake to 0.5 gm. An attempt was made to divert the excretion route for calcium from urine to stool by binding calcium in the intestine.* Edathamil, 4 gm. daily, was given orally during the 26th and 27th weeks. A sharp increase in both urinary and fecal calcium appeared during the 26th week, while the total excretion of calcium dropped below average during the 27th week. The serum calcium fell to 13 mg/100 cc. The stool potassium increased from 2.9 mEq. per day to 8.3 mEq. per day. The patient developed lassitude, and his serum potassium fell to 2.5 mEq. per liter. This was corrected by oral potassium salts. Oral edathamil, 4 gm. per day, was repeated during the 31st and 32d weeks. Total calcium loss did not change; but stool calcium increased, and urinary calcium losses showed a moderate decline. At this time reports on renal tubular damage due to edathamil appeared[12] and the drug was discontinued.

The patient appeared in good health despite the continued excessive calcium wastage. Tibial osteoporosis was noted on x-rays, however. His serum

* The chelating agent, sodium edathamil (EDTA or Versene) binds calcium[10] and is absorbed in negligible quantities when given orally.[11]

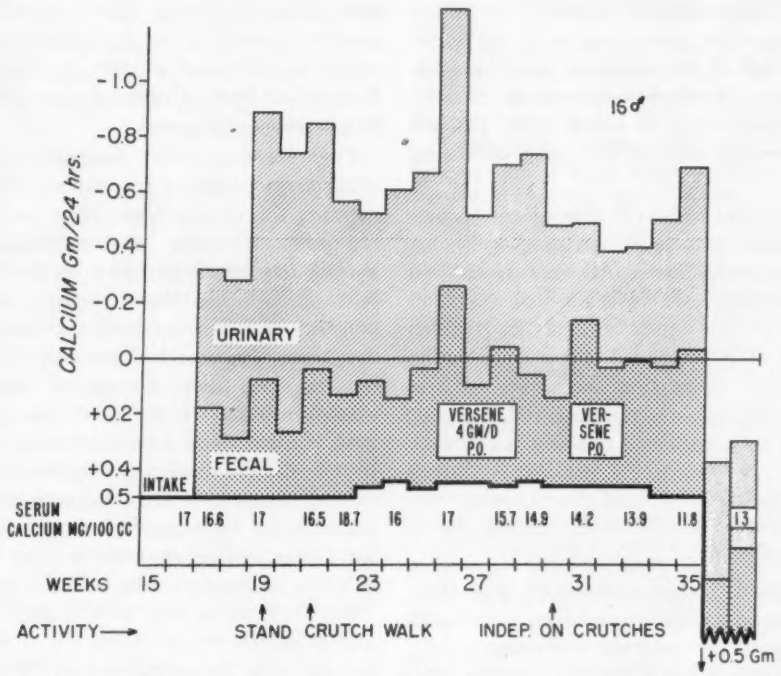

Fig. 4.—A balance study of the effects of mobilization on calcium metabolism in "pseudohyperparathyroidism" (case reported in text). The fecal calcium and urinary calcium excretion remained relatively constant during progressive mobilization, although the serum calcium gradually returned toward normal levels.

calcium dropped to 11.3 mg/100 cc. on the 35th week. The PSP dye excretion rose to 55%. A second intravenous pyelogram was normal. The hypertension gradually disappeared.

Dietary intake was raised to 1.5 gm. of calcium on the 36th and 37th weeks. Stool calcium rose to 710 mg. and 840 mg. per day during these two weeks, while urinary calcium averaged 410 mg. per day during the first week and 380 mg. per day during the second week. He was in positive calcium balance during both weeks but the serum calcium rose to 13.1 mg/100 cc.

On the 38th week he was discharged home, with instructions to take a 1 gm. calcium diet, to return to school. It was not possible to get follow-up laboratory data, but he remained well and now (January, 1957) is attending college in another state. He is still totally paraplegic.

Comment

Many workers[13-21] have recommended active exercises, physical therapy, and mobilization in wheel chairs to reduce hypercalciuria and renal-stone formation in paraplegic and fracture patients. In adolescents and young persons where acute demineralization with elevated serum calcium follows immobilization, remobilization has been considered mandatory to prevent serious sequelae.[6,8,9] The value of mobilization procedures in pseudohyperparathyroidism has been through inference because of clinical improvement but has been supported by very little quantitative calcium excretion data. In Albright's adolescent patient, during a 0.6 gm. diet, urine calcium still exceeded 1000 mg. per day one month after mobilization.[6]

Dietrick, Whedon, and Shorr[21] showed that normal men immobilized in body casts develop moderate to marked hypercalciuria. The urinary calcium excretion was lessened in these same men when they were similarly placed in casts but treated with passive mobilization on an oscillating bed.[22] One person from this group with the most

marked hypercalciuria repeated the initial response when again put in a cast without the use of the oscillating bed. Whedon and Shorr, however, were unable to alter the hypercalciuria in poliomyelitic patients by either the slow or the rapid oscillating bed.[23]

Whedon and Shorr [23] carried out further and extensive metabolic balance studies on poliomyelitic patients. All patients reduced their negative calcium balance or went into a positive calcium balance at about seven months after illness. A direct ameliorating effect of ambulation on the negative calcium balance was not observed, however. It was not possible to compare the calcium balance in comparably paralyzed subjects who were mobilized at different times, since only seven patients were studied during convalescence.

Freeman [24] made a semiquantitative study of urinary calcium excretion in paraplegics. Dietary intake was not controlled rigidly. No significant fall in calcium excretion after the institution of physical therapeutic exercises or the use of the wheel chair was found. Ambulation on crutches, however, was reported to be followed promptly by amelioration of the hypercalciuria. Freeman stated that the mere standing of debilitated paraplegics on crutches promptly lowered calcium excretion. Only a limited amount of data was provided in support of this statement, however, so that it is difficult to compare Freeman's results with the present ones.

The only previous quantitative study in neurologic patients specifically contrasting the effects of therapeutic mobilization and immobilization was that of Wyse and Pattee.[25] The effects of the oscillating bed and of weight bearing on the tilt table were studied in five paraplegics in varying states of general health. Two of the five subjects had decubiti at the time of study, and one had progressive carcinomatosis. Total calcium balance was carried out. No immediately favorable effects on either hypercalciuria or a negative calcium balance were observed during either oscillating or standing periods. The study was not designed to determine whether the long-term duration of hypercalciuria was modified by this passive mobilization.

The present study demonstrates that artificial mobilization by rocking, physical therapy, sitting in a wheel chair, or standing on a tilt table or crutches has no immediately beneficial effect on the hypercalciuria which follows acute paralytic poliomyelitis. There also was no indication that these measures had any definite effect on the long-term pattern of excessive calcium wastage which follows paralytic illness. In the young adolescent with pseudohyperparathyroidism vigorous mobilization did not reverse the hypercalciuria but was accompanied by a gradual amelioration in the degree of the hypercalcemia and hypercalciuria. Thus the serum calcium decreased from 18 to from 11.0 to 13.5 mg/100 cc., and urine calcium excretion fell to 400 mg. per day from the initial level of 700 to 1100 mg. per day. Several months were required for these changes to occur. We have observed similar changes in quadriparetic patients over the same period of time without employing such vigorous remobilization.

Normal persons produce nearly constant skeletal-muscle activity throughout both waking and sleeping hours and continuously exert tension on bones and joints by this mechanism. It may be, therefore, that the forces exerted on bones by therapeutic mobilization are physiologically negligible when compared to the extensive loss of stress and strain produced by the paralysis. Some aspects of the mineral metabolism of paralyzed patients are difficult to explain solely on the basis of loss of muscular and postural stress and strain on bones, however. Even in the absence of paralysis, mobility can be quantitated. It is not clear why patients with tuberculosis fail to lose abnormal amounts of calcium when given bed rest,[26] while patients suffering from poliomyelitis with minimal paralysis and

essentially no bed rest do have intense hypercalciuria.[1] Also, it appears to be more than a difference in mobility which is responsible for patients placed in unilateral leg casts for Achilles tenotomy [27] losing more calcium than is lost by healthy males immobilized in plaster from the waist down.[21] Finally, although the quantitative differences between passive standing or crutch-walking and normal activity are admittedly great, it is a little surprising that therepeutic mobilization produces no decrease at all (and at times may even produce an actual transient increase) in mineral loss. Thus other metabolic factors appear to contribute to the intensity and duration of the hypercalciuria seen in paralyzed patients. Effective measures to ameliorate or reverse the inexorable calcium loss which follows paralytic poliomyelitis will probably have to await clarification of these additional metabolic factors.

Summary

The effects of therapeutic mobilization on hypercalciuria were studied in 37 extensively paralyzed subjects with poliomyelitis. Therapeutic mobilization failed to induce any immediate amelioration of the hypercalciuria and failed to shorten the duration of the hypercalciuria among these subjects. In patients who were fully ambulated, the time of return of calcium excretion to normal was related more to the muscular capacity for walking than to the act of walking itself. The stress and strain on bone produced by therapeutic mobilization short of walking may be quantitatively too little to counteract the effects of paralysis on mineral metabolism. In addition, there appear to be other, unexplained, factors which supplement immobilization in initiating and maintaining the hypercalciuria which follows poliomyelitis.

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Some Metabolic and Nutritional Changes Associated with Injury

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A. Introduction

An understanding of the metabolic response to injury is of basic importance to medicine. It is the aim of this paper to present some known facts about the mechanism and significance of some of the metabolic reactions to injury and to point out a few of the gaps in our information which seem to us susceptible to present-day research techniques.

The usual features of the early metabolic response to injury of previously normal patients may be summarized as follows: increased heat production; weight loss; negative nitrogen, potassium, and phosphorus balances; disturbed carbohydrate utilization; tendency to ketosis; retention of sodium, chloride, and water, and a derangement in the metabolism of water-soluble vitamins. These changes are also usually accompanied by involution of lymphoid tissue and thymus, lymphopenia and eosinopenia, leukocytosis, adrenal cortical hypertrophy with associated depletion of cholesterol and ascorbic acid, and an increase in certain adrenal hormones (medullary and cortical) in the blood and urine. Liver function is altered, as evidenced by an increase in sulfobromophthalein retention and a decrease in the rate of conjugation of adrenal steroids. The metabolic reaction to injury, then, consists of a variety of chemical and physiologic changes which involve protein, carbohydrate, fat, water, vitamin, endocrine, and electrolyte metabolism in almost every organ of the body. These changes are qualitatively similar in patients with a wide variety of injuries or illnesses. In general, the intensity of the metabolic response parallels the severity of the injury but is most marked in previously healthy well-nourished young adult males. The response is dynamic, with an ever-changing, but generally predictable, pattern. Though all metabolites seem to be involved, the extent and duration of their involvement vary—sodium disturbances are brief; protein changes, prolonged. Finally, with recovery, after variable transition periods there is a return to normal.

Present evidence best supports the idea of a dynamic interchange of most body constituents. Borsook and Keighley[1] are generally considered the initiators of this concept of protein metabolism, and Schoenheimer,[2-4] Whipple,[5] their co-workers, and others developed the picture of a dynamic steady state between body proteins. This thesis rests on three possible continuing processes: (1) Proteins are completely degraded into amino acids, which are then resynthesized into new proteins; (2) proteins could be partially degraded to peptides which would then be reassembled into different proteins, and (3) synthesis of certain proteins could occur by transformation of existing proteins.[6] Only the first process has firm support to date.

Schoenheimer, Rittenberg, and associates demonstrated with labeled amino acids that the structure of a protein is not fixed but that there is continuous interchange between its amino acids and the free amino acids of its environment. The rate of interchange varies with the protein involved. In order

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to maintain this apparent steady state, there must be a very precise balance between protein synthesis and degradation. Thus, although an analysis of a body protein on two successive days will reveal the same amino acid composition and molecular arrangement, these amino acids are not necessarily the same ones of the day before. Within a few hours after the administration of labeled amino acids, the marked nitrogen can be found in all tissues; excreted nitrogen is not solely of dietary origin but is partly derived from tissue proteins. The concept of continuous replacement of most proteins in the body without an over-all quantitative or qualitative change is a most important one. This steady state is altered so that there is an eventual loss of body protein after injury.

Although protein metabolism is an area of the metabolic reaction to injury which has received much attention, it should be stressed at the outset that all metabolites are interrelated and, in the final analysis, all must be considered together. The metabolic alterations after injury involve not only protein but apparently all of the metabolites in the body.

The healthy adult male eats about 2500 Cal. and 60 to 100 gm. of protein per day. Thus, around 15% of the calories are supplied by protein, representing an intake of about 10 to 15 gm. of nitrogen daily. One to two grams of nitrogen are lost in the stools, while nine to thirteen grams are excreted in the urine. Following injury, fecal nitrogen is unchanged (unless there is specific gastrointestinal tract damage) but urinary nitrogen increases, at times to as much as 45 gm. daily. Urea is the principal component; proteinuria is slight. Urinary nitrogen reaches a peak about one week after severe injury and may continue high for three to seven weeks. Thereafter urinary nitrogen decreases and food intake usually increases, resulting in a positive nitrogen balance which continues until complete recovery.[7-12]

Early after injury there may be changes in plasma protein concentrations due to shifts and losses of water, electrolytes, and the plasma proteins themselves; the albumin fraction usually accounts for most of the loss. Such changes are most marked in patients with severe burns. If shock is severe, there is often a decrease in prothrombin and fibrinogen concentrations. Late after injury, plasma protein concentrations may be low as part of the generalized tissue protein depletion. Again the albumin fraction is chiefly decreased. The changes in other protein fractions are variable, depending on the presence of infection, liver dysfunction, and the like.

Hyperglycemia, lactacidemia, pyruvicacidemia, and acidosis may appear soon after injury and persist over a period of days or weeks. At times, there is some decrease in glucose tolerance and some resistance to insulin. These changes appear to reflect an increase in gluconeogenesis and in peripheral carbohydrate breakdown.[13,14]

Braasch and his associates[15] found an increased uptake of C^{14} by the perirenal fat of burned rats as compared with that of controls when methyl-labeled sodium acetate was injected intraperitoneally.

Moore and his associates[16] have demonstrated a rapid loss of body fat during the early postinjury period in patients on relatively low dietary intakes. Ketosis has also been described. Is there a specific increase in fat oxidation, or is this a nonspecific reflection of an inadequate caloric intake? This will be discussed later in Section B, 2.

Decreases in plasma ascorbic acid concentration, its urinary excretion (not followed by a period of increased loss), and "tissue saturation" as measured by intravenous "load tests" occur early after injury and may persist far into convalescence. The severer the injury, the greater these disturbances. Similar changes in urinary excretion and "tissue saturation" have been reported for thiamine and nicotinamide.[17,18] There is also a decrease in urinary excretion of riboflavin early, which, at times, is fol-

lowed by a brief period of increased excretion of riboflavin. Later, during the convalescent period when the patient is in positive nitrogen balance, there is also a positive riboflavin balance. No information is available regarding the fat-soluble vitamins.

Severe injury may cause sudden disturbances in water and electrolyte metabolism. These disturbances will be very briefly mentioned here, as they are detailed elsewhere.[19,20] For example, the early migration of fluid into, adjacent to, and from the injured area has long been recognized; there may be a general increase in measured extracellular space; serum sodium and chloride concentrations drop in the early post-injury period; there is a shift of sodium into injured cells, with a concomitant outward shift of potassium. Sodium and chloride excretions are initially low, resulting in early positive balances, but later, during the period of resorption of wound edema and diuresis, these balances transiently become negative. Generally, the periods of these changes are considerably shorter than those of the changes in protein metabolism. Potassium balance is usually negative for the early days after injury but becomes positive as potassium intake is recommenced. Apparent correlation between nitrogen and potassium balances is variable—at times there is, early, relatively more potassium lost than would be expected from the known potassium-nitrogen ratio in normal tissue. Also, potassium balance may become positive sooner than nitrogen balance. At other times, the potassium and nitrogen balances are more nearly parallel.

Less is known regarding other electrolytes. The few studies of sulfur metabolism have indicated a close relationship to protein. Increased urinary excretion of calcium may occur early after injury, particularly if bones have been fractured.

Limited information is available regarding altered enzyme resulting from injury.[21] Some of the reported changes are an increase in proteolytic, lipase, and phosphatase activity in the lymph draining a burned area; an increase in plasma fibrinolysis in severe shock, and a decreased ability of liver slices from burned rats to deaminate alanine or to make glycogen.

Little is known of the effect of trauma on the various nucleoprotein metabolites of tissue and blood. This lack of information is a reflection of a corresponding lack of methods whereby these compounds may be fractionated from biological materials and quantitatively measured. Green and his associates [22] have described changes in nucleotide metabolism in trauma as measured by increased plasma levels of certain pentoses. They have also shown that certain nucleotides, such as adenosinetriphosphate (ATP), adenosinediphosphate (ADP), and adenosinemonophosphate (AMP), induce a shock-like state in rats when injected under certain conditions.

B. Mechanisms of the Early Changes in Protein Metabolism Following Injury

1. *Absorption and Excretion of Protein Breakdown Products.*—It is important to differentiate between two mechanisms of protein catabolism. One is local release of protein and its metabolites from injured tissue; the other is systemic protein breakdown. Autolysis and the absorption of tissue protein breakdown products from the injured area account for a part of the increased urinary nitrogen, but its contribution to the total has not been assessed. While the metabolic reaction to injury has been described as a catabolic reaction (connoting an over-all breakdown of body proteins), each tissue protein actually anabolizes and catabolizes at its own unique rate. As mentioned, these reactions proceed at such rates in the healthy adult that a "steady state" results. The anabolic and catabolic reaction rates change after injury in a manner peculiar to each tissue protein. For example, wound healing, a net anabolic process as a rule, begins while the patient is still in an over-all net negative nitrogen balance.

Munro and his co-workers [23,24] have thrown some light on these obscure metabolic relationships. They fed rats a protein-free diet until their nitrogen excretion was constant. When these protein-depleted rats were injured (femoral fractures), they failed to develop the usual "normal" catabolic response. They explained this by postulating the existence of "storage" protein as well as "essential" protein and felt that it was the "storage" protein which was lost following injury. Accordingly, when "storage" protein was depleted prior to injury, no increase in excretory nitrogen would occur following severe injury. Whipple [5] has differentiated body protein into (*a*) fixed or indispensible cell protein, without which cellular life ceases; (*b*) "dispensible" protein, which can be yielded up by the cell as a source of energy during starvation, and (*c*) "labile" protein, which can move in or out of the cell as plasma proteins rise or fall. In recent years, studies with isotopically labeled compounds have demonstrated differences in the metabolic turnover of various tissue proteins, but the sharp physiologic differences implied by the descriptive terms "storage," "fixed," "dispensible," and "labile" are not clearly established.

Madden and Whipple [25] became interested in the problem of whether the increased urinary nitrogen following injury reflected increased tissue breakdown or decreased tissue build-up. They also wondered what tissues are involved and to what extent. Using S^{35}-labeled methionine, they investigated the effect of turpentine abscesses on the urinary excretion of sulfur and its incorporation into the plasma proteins and other tissue proteins of dogs. The calorie, organic nitrogen, and sulfur intakes were constant. Tagged methionine was given one day after the injection of turpentine, and the dogs were killed 24 hours later. There was an increased urinary output of both sulfur and nitrogen as compared with control dogs, but no increase in urinary excretion of S^{35}. The appearance of S^{35} in various tissues was generally comparable in terms of specific activity in the dogs with abscesses and in normal dogs, although there was a distinctly higher activity in the plasma protein of the dogs with abscesses.

Levenson, Braasch, Mueller, and Crowley [26] carried out similar studies in normal and burned rats with use of N^{15}-labeled glycine. When healthy rats were deeply burned over one-third of their surface area, they showed excessive urinary nitrogen losses, which peaked about 3 to 4 days after injury and gradually returned to normal in 14 to 16 days. By the use of tube feedings, dietary intake was kept constant at a level such that the adult rats (about 275 gm. in weight) were in slight positive nitrogen balance during the control period. After the burn, fecal nitrogen was unchanged but urinary nitrogen excretion increased. At the height of the period of negative balance, a tracer dose of N^{15} glycine was given orally with the regular diet; the rats were killed 12 hours later. The proteins of various tissues were isolated and their N^{15} and total nitrogen contents, measured. Groups of burned and control rats were studied simultaneously.

The incorporation rate of N^{15} was least in the skin and carcass proteins of the control animals and greatest in the liver, gastrointestinal tract, and plasma proteins. The same distribution of incorporation rates was observed in the burned rats and in all cases was equal to or greater than the corresponding rates for the tissues of control animals. If the incorporation of N^{15} signifies synthesis, anabolism was occurring in the burned rats; the increased urinary nitrogen cannot be explained by antianabolism solely.

In another experiment, the N^{15} was given over a period of four days to label the tissue proteins of rats. One group of these rats was then burned, and another group, used as controls. The rats were then killed at various times, and the N^{15} content of the tissues was compared with the N^{15} content of rats which had been killed at the end of

the four-day tagged-feeding period. The burned rats were found to have lost significantly more N^{15} from their plasma protein than did the unburned. But it was found that the protein content of organs such as the liver changed little despite their markedly increased turnover rates in burned animals, while the carcass, despite a much slower turnover rate, lost a great deal of protein, which accounted mathematically for most of the increased urinary nitrogen loss. Little is known about this subject in man. Blocker [27] used S^{35}-labeled methionine and found increased incorporation of S^{35} in the plasma proteins of burned patients. He also states that catabolism proceeds at an even greater rate elsewhere—with the net result of body protein depletion. Moore [28] has pointed out that the amounts of nitrogen lost by the severely injured patient may be so large that its source must almost certainly be the skeletal muscle; the muscle wasting which frequently occurs following injury is readily apparent on physical examination.

2. *Increased Oxygen Consumption and Heat Production.*—Little is known about the actual total oxygen consumption and heat production by the injured patient. Limited measurements of "basal oxygen consumptions" indicate that the metabolic rate is increased. Often the urinary nitrogen and oxygen consumption follow similar courses. Cope et al.[29] have speculated that since there is so much cellular and chemical activity in the injured areas the rate of oxygen consumption may be increased in these areas and that it is this increase in local activity which determines, in part, the apparent increased activity in metabolic rate of the severely injured patient. In this regard, they point out the correlation of the increased over-all metabolic rate with the extent of the wound area in the burned patients. However, specific information on the actual metabolic rate of the injured areas or other specific tissues is not available. Muus and Hardenbergh [30] have observed that the oxygen consumption of normal rat liver slices is increased when incubated in lymph from the burned legs of calves and dogs.

Fever is known to influence the rate of oxygen consumption. For each degree (Fahrenheit) rise in temperature, there is a 7% increase in the metabolic rate. Although fever probably plays a role in the elevated metabolic rate of the severely burned patient, Cope et al. observed that the temperature rises in the patients were irregular and did not correlate with the metabolic rate.

Cairnie [31] and his colleagues have recently studied the increase in total metabolism in rats given a constant high-protein diet (20% protein), as measured in a gradient-layer calorimeter. With this instrument it was found that the metabolism rapidly rose to a peak on the third day after fracture and this was followed by a more gradual decline. This change paralleled the characteristic curve of urinary nitrogen excretion. The heat production due to protein catabolism was calculated from the urinary N excreted by rats with fractures kept outside the calorimeter under the same conditions of dietary intake. (The calculation assumed that the nonprotein residues were oxidized for energy.) When this quantity was set alongside the data for the total metabolism, close agreement was found both in the magnitude and in the duration of the observed and calculated increases in heat production. On this close agreement, Cairnie and his associates feel that following fracture the whole of the increase in heat production has its origin in increased protein catabolism and not in increased fat and carbohydrate catabolism. This observation of Cairnie is very important; additional investigation in this area is clearly indicated.

3. *Inactivity.*—Inactivity is one of the causes of tissue protein loss in patients with severe injury. Ries, in 1899,[32] first reported the benefits of early rising after surgical procedures. Since then, the advantages and disadvantages of early physical activity as a therapeutic measure have been much debated. There are, however, few studies

which yield information concerning the effects of bed rest and exercise on the metabolism of patients suffering from injury or disease. Deitrick and his associates [33] observed healthy young men before, during, and after a prolonged period of bed rest. The subjects ate a constant diet adequate to maintain them near nitrogen and mineral equilibrium during the control period. During this time, they were ambulatory and took daily exercises consisting of calisthenics, swimming, and walks. During the bed-rest period, activity was limited by immobilization of the pelvis, girdle, and legs in plaster casts extending from the umbilicus to the toes. During the six- to seven-week period of bed rest, all the subjects were in negative nitrogen balance and each lost, on the average, a total of 54 gm. of nitrogen (equivalent to about 1730 gm. of tissue). Calcium losses ranged from 9 to 24 gm., and there were also increased excretions of phosphorus, sulfur, sodium, and potassium. Other changes noted were a decline in basal metabolic rate during immobilization, averaging 7%; small changes in body weight; a significant decrease in muscle mass and muscle strength of all extremities; marked decrease in exercise tolerance as measured by the response of the pulse rate to the Master step test, and an average increase of four beats per minute in the resting pulse rate.

Searching for methods which could be instituted without delay to combat the deterioration of bed rest, one year later Whedon [34] and his group employed the Sanders oscillating bed. (This bed rocks slowly back and forth, raising the heaad and lowering the feet through a total excursion arc of 24 degrees, one complete cycle of oscillation requiring one and three-fourths minutes.) This experiment was conducted under the same conditions and using the same subjects as in their previous study,[33] except that immobilization was carried out in an oscillating bed rather than the usual fixed hospital bed. The authors found that the use of the oscillating bed reduced the loss of nitrogen and calcium by approximately 50%, significantly decreased the excretion of phosphorus, and, in general, largely prevented deterioration of the physiologic functions. They postulated that, although the mechanism by which the oscillating bed serves to reduce the effects of immobilization is not clear, the principal factors might be an increased circulation through the extremities and partial weight-bearing in the foot-downward position. They suggest the skeletal stress so produced stimulated slight muscular contractions which may discourage catabolic and encourage anabolic processes.

Glickman and his associates [35] have reported the effect of early bed exercise of a calisthenic type combined with ambulation on nitrogen metabolism in patients subjected to relatively minor operative trauma (herniorrhaphy). A control period of six to seven days before surgery was devoted to stabilization of diets, to tests, and to prescribed exercises. The exercised patients were allowed out of bed on the first postoperative day. In those patients fed basal calories plus 20% (15% of the calories derived from protein), a nitrogen deficit of about 31 gm. occurred in each member of the control group during the first six postoperative days, while in the exercised group the nitrogen deficit was about 23 gm. In these patients tube-fed a high protein diet (basal calories plus 20% with 40% of the calories derived from protein), an average nitrogen balance of +6 gm. was maintained in each of the control group and +19 gm. in the exercised group. Unfortunately, the metabolic periods were short in this study. The effect of early exercise on the metabolic responses to injury warrants further investigation.

4. *Endocrine Factors.*—There is evidence that the metabolic reaction to injury may be mediated in part through the neuroendocrine system. Early impetus for this view came from the observations and writings of Claude Bernard, Walter Cannon, and Hans Selye. The state of adrenal function was

noted to influence profoundly the capacity of the organism to respond to stress. An abrupt increase in adrenal medullary activity following injury was demonstrated early. Later, Selye reported tissue disintegration, cellular atrophy, and even necrosis in various tissues, with the notable exception of the adrenal cortex, which, on the contrary, almost invariably hypertrophied. These histologic changes in the adrenal have since been correlated with an early increased secretion of certain adrenal cortical steroids as measured by increases in urinary and blood steroid products. Many manifestations of the stress reaction were not found in adrenalectomized animals. It was further noted that the resistance of adrenalectomized animals to exogenous stressors is low; this confirmed what clinicians had long known about patients with Addison's disease.

A relationship between the pituitary and adrenals in the physiologic response to stress was demonstrated in the early studies. It was known by 1920 that adrenal cortical atrophy occurred after hypophysectomy. Selye predicted and observed that hypophysectomy, like adrenalectomy, prevented the usual reactions to stressing stimuli. Extension of these observations led Selye to formulate his concept of the "general adaptation syndrome."[36,37] Later observations showed that ablation or stimulation of certain areas of the hypothalamus either depress or activate the secretion of corticotropin (ACTH). Apparently the hypothalamus activates the anterior pituitary humorally. There has been much discussion about how the hypothalamic-pituitary-adrenal system is activated.[38-40] Both nervous and metabolic factors are involved.

Since the concepts of the general adaptation syndrome and, more recently, the local adaptation syndrome have been discussed so frequently and fully elsewhere, they will not be elaborated here. Almost all metabolites are affected by the various pituitary and adrenal hormones, though the precise manner in which these hormones modify metabolic reactions is not known. It seems clear that they do not initiate new reactions. After injury, certain hormones are apparently secreted in amounts that are capable of causing metabolic upsets when given in nonstress situations. Many of the biochemical responses seem to be related to the presence of an injury of a certain severity rather than to one of a specific type and, in this sense, seem nonspecific. Since many of these metabolic changes are similar to those induced by administration of certain adrenal hormones, increase in adrenal activity has been considered important in the pathogenesis of the metabolic reaction to injury. This thesis has gained some support from the findings that (1) many of these changes do not occur in the unsupported adrenalectomized animal and (2) some of the metabolic changes and the apparent adrenal cortical hormone excretion roughly parallel the severity of the injury. However, certain studies have demonstrated the occurrence of some of the biochemical changes associated with injury in the presumed absence of any concomitant increase in adrenal hormone production.

Ingle, Ward, and Kueziga[41] and Toby and Noble[42] found the same increase in urinary nitrogen excretion following fractures in adrenalectomized rats that were given maintenance adrenal cortical extract and in sham-operated-on controls; no increase was found in adrenalectomized rats maintained with saline solution. Ingle concluded that the negative nitrogen balance resulting from injury requires the presence of adrenocortical hormones but is not specifically caused by an increase in their secretion. Campbell[43] confirmed this work with cortisone instead of adrenocortical hormone. Engel[44] came to the same conclusion. Similar observations of the occurrence of hyperglycemia following diethylstilbesterol administration or traumatic shock[45] have been made.

Ingle calls this the "permissive" or "supporting" action of the adrenocortical hormones, and Selye, from a different point of view, speaks of the "conditioning" action of

these hormones. Certain responses to the adrenal steroids are modified by associated systemic stress.[46] This may result from a decrease in conjugation of circulating steroids by the liver or a change in target tissue reactivity. Further, the possibility exists that in adrenalectomized animals given maintenance doses of adrenal hormones, accessory adrenal tissue may respond to trauma with increased activity.[48] We shall have to await the measurement of steroid activity and secretion in injured animals for clarification of these points. It is generally accepted, however, that there is an association between the extent of metabolic response and the level of cortical hormones secreted. The level of adrenocortical hormones which are necessary in adrenalectomized animals for the full metabolic reaction depends on the severity of the injury. The specific nature of the relationship between biochemical changes resulting from injury and adrenal activity is not known. Studies of specific tissue metabolism will probably be required to establish this.

Considerably less information is available regarding the behavior of the other endocrine glands after injury. There is an increased secretion of antidiuretic hormone (ADH), which doubtless affects renal function.[47] ADH may be one of the mechanisms whereby the secretion of corticotropin is stimulated.

While the presence of active thyroid hormone seems necessary for the usual metabolic response to injury, it is not certain that thyroid function is increased. This possibility has been considered in view of the elevated oxygen consumption by injured patients. Cope and his associates[29] measured protein-bound iodine concentrations in the serum and the uptake of I^{131} by the thyroid in some burned patients. No significant changes in these measurements were observed, early or late. All patients were considered to have been euthyroid prior to injury.

For several years, Goldenberg and his associates[48] have been attempting to assess the role of the thyroid in the metabolic reaction to operation. Measurements of I^{131} uptake by the thyroid, I^{131} urinary excretion, and protein-bound I^{131} have been made, with particular emphasis on the period of operation and the very early postoperative period. They interpret their data as indicating a brief increase in thyroid activity immediately after operation in previously well patients, but the evidence presented is not conclusive.

5. *Inadequacy of Food Intake.*—Inadequate food intake is one of the most important causes of negative nitrogen balance resulting from severe injury. Nitrogen loss is accentuated by reduced food intake. The seriously injured patient frequently has a poor appetite that is worsened by oversedation, apprehension, and pain. Further, alterations in gastrointestinal function may occur soon after severe injury, particularly if the patient is in shock or there is intra-abdominal damage. It is important to remember, however, that the reduction of food alone does not account for the increased urinary nitrogen excretion, as Wilkinson[49] and others have shown clearly. An increased urinary nitrogen excretion is seen even when food intake is maintained at a preinjury normal level. However, the net nitrogen loss is less when food intake is high than when the dietary intake is low. The diet should be nutritionally complete to minimize excessive nitrogen loss, for a deficiency in the intake of one nutrient affects all others.

6. *Other Factors.*—An increase in various proteolytic enzyme activities has been demonstrated in the blood, lymph, and tissues of burned animals and humans. The significance of these findings in relation to nitrogen metabolism has not been studied. The possibility was suggested a number of years ago that a specific disturbance in amino acid metabolism might be an important factor in the metabolic reaction to injury. There is no conclusive information substantiating this view. Now that a practical method for the quantitative fractionation of amino acids is available in ion-exchange chromatography, we can anticipate more information on amino acid metabolism in the near future. Levenson, Howard, and

Rosen [50] have found that the total plasma amino acids measured individually by ion-exchange chromatography usually remain normal following severe injury even in the presence of serious renal failure. Some of the individual amino acids increased, while others fell. However, these individual fluctuations were small compared with the rise in other nonprotein nitrogen substances. The only notable free amino acid rise in the plasma seen by these investigators was in alanine following burns. It is of interest, in this regard, to notice that van Bekkum and Peters [51] have reported that liver slices taken from animals in shock do not deaminate alanine as rapidly as normal. Patients with liver disease show few abnormalities of plasma amino acids until the last stage of hepatic failure. There was an amino acid conjugate fraction which rose after injury; this will have to be investigated further.

Some disturbance of liver function is not uncommon in extensively injured patients, particularly if shock has been severe. Increased sulfobromophthalein (Bromsulphalein) retention, increased urine urobilinogen excretion, increased serum bilirubin concentration, abnormal cephalin flocculation, and increased prothrombin time have been described. These changes are most marked in the early period following injury and are related to the severity of the trauma.[52]

C. The Significance of the Metabolic Reaction to Injury

The innumerable descriptions of the biochemical changes which occur soon after injury give little objective data of their clinical effects. Thus, it is not surprising that opinions differ as to the significance of these early metabolic derangements. Cuthbertson has recently reiterated his viewpoint in a general review of this problem.[53]

> As long ago as 1794, John Hunter wrote with a rare perception: "There is a circumstance attending accidental injury which does not belong to disease—namely, that the injury done has in all cases a tendency to produce both the disposition and the means of cure."
>
> From teleological considerations the present writer early suggested that the general reaction by which labile protein is catabolized as the result of injury may serve to provide energy or amino acids, or both, for the healing process, and that this is a primitive response independent of food, for a wounded animal is necessarily reduced in its capacity to feed itself. Glycogen and fat depots will also be involved. . . .

Whether or not attempts are made to correct the early metabolic derangements depends on one's viewpoint. It has seemed to us that there is a need for objective information of the clinical and physiological significance of precise changes. In particular, systematic observations of wound healing should provide some objective evidence in one important area of the significance of the metabolic upset and thereby serve as the basis for suitable prophylaxis and therapy.

It is well known that wound healing of obviously malnourished patients is impaired; while there is no significant delay in the rate of sloughing of dead skin in nutritionally depleted patients with full-thickness burns, there is a marked delay in wound closure. Skin grafting is often unsuccessful, and donor sites fail to heal.

But what of the healthy and well-nourished person who suddenly enters the period of profound metabolic alterations consequent to a severe injury? How do the wounds of such a patient heal in the early period after injury before gross nutritional abnormalities are evident? Studies bearing on this problem have been carried out in animals by the use of tensile-strength and histologic measurements of experimental wounds. Several investigators have found delayed wound healing in the early postinjury period in various animals. These studies have not yet been extended to man.

It is possible that the abrupt changes in protein metabolism which occur very soon after injury in patients with severe injuries and continue for several weeks may well effect wound healing. Further investigation of specific amino acid metabolism following injury is indicated from this point of view, since certain amino acids (e. g., the sulfur

amino acids) seem to be particularly important in healing.

In certain species an increase in some adrenal hormones brought about by various means, including the injection of corticotropin and cortisone, significantly modify inflammatory reactions and affect wound healing. The effects vary according to the agent, dosage, time, ..te, route of administration, etc. In general, the histologic changes are similar to those seen in the protein-deficient animal—the primary delay seems to be in production of capillaries and fibroblasts and, as related phenomena, the production of intercellular substances.

The mechanism of the cortisone effects on wound healing is still a subject for debate. Perhaps these effects are related to the effects of the adrenal steroids on protein metabolism in general, i. e., an apparent decrease in protein synthesis with a smaller effect on protein catabolism. They may act systemically, perhaps by antagonizing the pituitary growth hormone, or locally, by retarding cell growth directly. Baker [54] has shown that the local application of cortisone in amounts too little to induce measurable systemic effects will delay healing at the site of application. Lattes and his co-workers [55] have suggested that under the effect of cortisone, injured tissues fail to release chemical substances necessary for the initiation and completion of repair. Menkin [56] has described extensive studies concerned with the chemical substances released following injury and during the inflammatory and healing process.

In view of these effects of some adrenal cortical hormones on healing, the possibility must be considered that adrenocortical hormones liberated in excessive amounts in the acute period after trauma may be partially responsible for the connective-tissue changes which occur in the wounds of the injured animals. Chassin and his co-workers, in particular, have championed this viewpoint.[57] They found that in young adrenalectomized rats, maintained with a small fixed dosage of aqueous adrenal cortex extract, skin excision (four days prior to laparotomy) did not result in depression of the bursting pressure of fifth-day laparotomy wounds, as is the case with nonadrenalectomized rats subjected to the same preoperative stress.

This observation, if it is confirmed, is not in accord with the concept that the increased secretory activity of the adrenal cortices during stress tends to maintain homeostasis rather than to cause hypercorticalism.

Certain vitamins, particularly ascorbic acid, are among the nutritional factors known to influence wound healing. There is an abrupt and sustained drop in blood and urinary ascorbic acid saturation as measured by intravenous load tests. Does this represent functional scurvy? A definite answer to this question might be obtained by capitalizing on the intimate relationship of ascorbic acid and wound healing. If the injured person is physiologically scorbutic, one should see alterations in healing characteristic of ascorbic acid deficiency. Accordingly, Levenson, Upjohn, Preston and Steer [58] studied the healing of abdominal incisions in normal and burned guinea pigs that received 2 mg. of ascorbic acid daily. This is the daily requirement of a healthy young guinea pig, one of the few animals which require exogenous ascorbic acid (vitamin C). The laparotomy wounds in the burned guinea pigs were grossly abnormal and the histologic changes were indistinguishable from those in unburned scorbutic guinea pigs. Fibroplasia was ample but disordered; hemorrhages were frequent; reticulum and "ground substance" (stainable metachromatically with toluidine blue and blue with colloidal iron) persisted for an unusually long time, while collagen formation was delayed. Neither the reduction of food intake nor administration of large doses of cortisone led to the altered histologic changes in guinea pigs. When we administered large doses of ascorbic acid (100 mg. daily) to the burned animals, their wounds healed normally. All this suggests that the severely burned guinea pig becomes physiologically scorbutic when he receives only that amount of ascorbic acid necessary for normal growth and heal-

ing of the uninjured animal. This demonstrates how one may deduce from metabolic studies prophylactic and therapeutic measures for the care of the injured.

The problem of wound infection is inextricably bound to wound healing, for impaired healing increases the probability of infection, and, conversely, infection delays healing. There is some evidence that animals have a lowered resistance to infection in the early period after severe injury, particularly if shock is present or has occurred. An abrupt drop in serum properdin level and an increased susceptibility to injected endotoxins or to injected bacteria have been observed under these conditions. Malt and Cope [59] found by measuring the disappearance rate of radioiodinated bovine γ-globulin that wounds, full-thickness burns, and exposure to cold did not alter antibody production in rabbits. However, a group of rabbits subjected to tibial fractures showed a significantly earlier and greater antibody response. The role of the adrenals in infection and particularly the role of cortical hormones has been discussed extensively elsewhere.[60]

Dubos [61] demonstrated that an abrupt withdrawal of food increased the susceptibility of mice to experimental infections. In a recent abstract, Dubos [62] stated:

> Albino mice were fed ad libitum diets differing in their contents in proteins, amino acids, and fat, but providing adequate caloric and vitamin intake. At different periods of time after being placed on the experimental diets the animals were infected with standardized dose of either one of three infectious agents: Staphylococcus aureus, Mycobacterium tuberculosis, Mycobacterium fortuitum.
>
> It was found that profound differences in susceptibility could be elicited by changes in the dietary regimen, even when the latter did not affect the weight curves of the non-infected animals. For example, mice fed commercial pellets (which are adequate for growth) were much more susceptible to Staphylococcus than were mice receiving a diet containing 20 per cent casein. A great increase in susceptibility to the three infections occurred when the casein content of the diet was reduced from 20 to 9 per cent, even though the uninfected animals grew well on the latter diet. When the complete diet was replaced by one containing gelatin as sole source of protein, the increased susceptibility took place within 2 days; normal resistance could be restored rapidly by adding casein in proper amount.
>
> Preliminary results indicate that the fat content of the diet is of great importance in determining the response of mice to experimental tuberculosis, but not to Staphylococcus infection.

The mechanism for these alterations in susceptibility to experimental infections is not yet known. Dubos [63] previously stated:

> Through a number of different mechanisms arrived at by evolutionary adaptation, man has achieved some sort of ecological equilibrium with the micro-organisms that are ubiquitous in his environment. Indeed these micro-organisms may be harboured in the body without causing disease, and establish relationships with the tissues—covering the whole gamut from the commensalism and symbiosis represented by the flora of the gut, to the various types of arrested or latent infections. The factors which determine whether the microbial agents are thus held in check, or undergo unrestrained multiplication, are of course highly complex. Metchnikoff had identified resistance to infection with the ability of the leucocytes to engulf and destroy infectious agents. It seems now that this mechanism, even though supplemented by various humoral factors, operates in but a very few types of infections. I have presented the view that natural and acquired resistance depends more often upon the ability of the inflammatory response to create in and around the lesion a micro-environment inimical to the infectious agent.
>
> It is likely that disturbances in the general state of health often bring about qualitative and quantitative changes in the biochemical characteristics of the inflammatory area. These in turn may interfere with the processes which control the activities of micro-organisms within the lesion. As a result, the response of the body to infection and consequently the micro-environment in which the infectious process follows its course, are under the control of factors which may be metabolic or psychic in origin. This concept accounts in part for the fact that susceptibility to infection can change independently of the immunological state of the infected individual. Since changes in susceptibility can occur rapidly, and be extremely transient the intensity of exposure to an infectious agent may be less decisive than the physiological state of the exposed individual, determining whether infection fails to take hold, becomes established, runs an abortive course, or evolves into overt disease.

There is no clear-cut evidence that the resistance to infection in the seriously injured patient is decreased. However, only limited information is at hand. Balch [64]

found no change in the phagocytic properties of peripheral leukocytes of soldiers who had recently been severely wounded. He also found no decrease in the rise of antibodies following injection of booster doses of tetanus toxoid into these soldiers. Further observations are clearly needed.

There may be increased susceptibility to additional trauma, anesthesia, etc. The specific relationship of these factors to the known metabolic changes has not been adequately clarified.

D. Conclusion

At present much of our knowledge of the widespread metabolic changes following severe injury is descriptive. With the development of new techniques, the future promises some answers to fundamental questions which plague us today. We have discussed some factors which clearly are involved in the metabolic reaction to injury, and we have presented some of the limited objective information pertaining to its significance. The significance of the various metabolic changes will have to be evaluated objectively on their own merits. A study of patients, their wounds, and their clinical courses (including resistance and response to infections, trauma, anesthesia) directed toward a broad correlation and evaluation of systemic and local phenomena is needed. Such a study will, of necessity, entail the use of a variety of techniques—clinical, metabolic, bacteriologic, and pathologic. Constructive prophylactic and therapeutic measures for the care of the injured patient will derive from these studies.

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Hyperplasia of the Palmar Aponeurosis (Dupuytren's Contracture)

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Introduction

Numerous attempts have been made to determine the cause of Dupuytren's contracture. The results can be classified as follows.

(1) *Trauma.*—Dupuytren, himself,[24] considered repetitive trauma of the handpalm to be the cause of the contracture. An investigation conducted on behalf of the British government among lace minders showed an incidence of 13.1% Dupuytren's contracture.[18] Three years later a similar inquiry found the rate to be only 1.7%, the discrepancy being attributed to the lower average age in the second group.[10] This opinion was supported by Gerritzen.[30] About 20 years later another investigation was unable to demonstrate that trauma was of any etiologic significance.[36] Niederland found four times as high an incidence in people whose hands underwent repetitive trauma in the course of their occupation as in those with less traumatizing work. When presenting this series he was supported by Baader, but also met with sharp disagreement.[64] He had examined only subjects over 40 years of age. It is of interest that the intensive study of Skoog [81] appeared to show that certain physicochemical changes of the palmar aponeurosis occurred in higher age groups, predisposing the fibrous bundles to rupture by trauma. Formation of scar tissue would be responsible for the characteristic nodules and contractures.

(2) *Neurogenic Origin.*—The possibility that the nervous system might be involved in the etiology of Dupuytren's contracture was first considered by Eulenburg, who observed its development in a case of ulnar neuritis.[26] Subsequently, Robert Abbe noticed the frequent association of neuralgic pain and paresthesia involving the neck and arms.[1] He based a theory on this observation, which postulated that a slight injury to the hand could create a tissue disturbance through a nervous reflex, which also could involve the contralateral extremity. Almost 50 years later this theory was supported by Maurer,[55] by Schaefer,[75] by Alajouanine et al.,[3] and by many others.[53,73,78] Injury to the ulnar nerve especially has been held responsible with a remarkable frequency.[14,16,44,45,65,71]

Disease of the cervical segment of the spinal cord has been regarded as an etiologic factor. The first case was one of syringomyelia involving the cervical portion of the spinal cord, reported by Bieganski in 1895.[9] Twenty such cases were collected from the literature in 1935,[89] and two more were described in 1947.[34] Other diseases of the central nervous system have been held responsible for Dupuytren's contracture, such as tabes dorsalis,[41,65,80] gliosis,[66] poliomyelitis,[23] pellagra,[68,69] and plumbism.[20,59] A number of studies have stressed the high rate of incidence in epileptics. Most of these patients had been treated with barbiturates. This treatment was believed to be the important factor by some authors.[6,41,81] On the other hand, Lund [51] strongly considered the possibility that an affection of the cortical vegetative centers might be responsible both for the convulsive disorder and the Dupuytren's contracture.

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Injury of the spinal cord also has been described as the origin of a Dupuytren's contracture.[65,70]

A number of authors have observed a Dupuytren's contracture following a myocardial infarction.[40,49,90] This suggests a pathogenic mechanism similar to that of scapulohumeral periarthrosis or the full-blown shoulder-hand syndrome that also may follow myocardial infarction.[4,5,11,19,25,76,86] Steinbrocker et al. regard Dupuytren's contracture as an "abortive" shoulder-hand syndrome.[86] Coste [19] groups Dupuytren's contracture together with the shoulder-hand syndrome and Sudeck's atrophy as manifestations of a "sympathosis," which may be provoked by stimuli such as trauma, cervical osteoarthritis, and myocardial infarct. It is interesting that Hansen found evidence of abnormal vegetative impulses in the hands in 5 of 27 patients with scapulohumeral periarthrosis by measuring skin temperatures.[35] Mogensen [60] made similar observations in three out of six patients. Lund [51] found a striking coincidence of scapulohumeral periarthrosis and Dupuytren's contracture.

(3) *Cervical Osteoarthritis.*—Lesions of the cervical spine have been mentioned with increasing frequency as part of the etiologic mechanism in the more recent literature. Trauma to the skull, the neck, and the dorsal spine was followed by development of Dupuytren's contracture in a case reported by Mainzer.[52] Padovani and Lord [67] found roentgenologic evidence of cervical osteoarthritis in 14 out of 23 patients; James and Tubiana,[39] in 13 out of 27 patients. Scholz [77] believed that the narrowing of the intervertebral foramina might irritate sympathetic fibers. This would result in a disturbance of the vasomotor mechanism, producing Dupuytren's contracture. Gutzeit [33] also postulated such a sequence of events. It is to be remembered that both Coste [19] and Steinbrocker [86] stated that cervical osteoarthritis could be instrumental in producing either the abortive or the full-blown shoulder-hand syndrome.

(4) *Metabolic Disorders.*—From time to time reports have appeared of an increased incidence of Dupuytren's contracture in certain metabolic disorders. Maréchal reported the association of Dupuytren's contracture with diabetes mellitus in 1899.[54] Davis and Finesilver supported this observation by comparing a group of diabetic patients with nondiabetic but otherwise comparable subjects and finding a higher incidence of Dupuytren's contracture among the diabetics.[22] A few cases were reported to have improved under treatment with thyroid substance,[48,91] although there was no evidence of hypothyroidism. A low blood tocopherol (vitamin E) level has been suspected of being causally related to Dupuytren's contracture.[83,84] Although the results of treatment of Dupuytren's contracture with vitamin E have been equivocal, this hypothesis recently received support. A high degree of correlation of cirrhosis of the liver and Dupuytren's contracture was observed. It was believed that the low blood tocopherol level incident to dysfunction of the liver might be the link between these two conditions.[91]

(5) *Miscellaneous Opinions.*—A number of authors believed that Dupuytren's contracture is a heritable disorder.[22,32,61,74,79,81] Krogius theorized that Dupuytren's contracture was a fibrous metaplasia of rudimentary brief flexor muscles of the hand.[43] Dupuytren's contracture has also been linked with rheumatism and gout [47] and with fibrositis.[88] However, the diagnostic concepts that formed the bases for these conclusions vary considerably from the accepted diagnostic criteria of today.

Hyperplasia of the Palmar Aponeurosis and Dupuytren's Contracture

Dupuytren's contracture is a disabling disorder of the hand. The earlier stages of this condition, where only thickening of the palmar aponeurosis is present or where one or more nodules can be palpated and the overlying skin has become "puckered" and adherent to the palmar aponeurosis,

frequently go unnoticed by the patient. Thus they also may escape the attention of the physician. Some authorities maintain that mere thickening of the palmar aponeurosis is a condition that is not necessarily related to Dupuytren's contracture.[31,81] However, the following case is an example of progression of simple aponeurotic thickening to contracture.

CASE 1.—A 59-year-old woman was seen in 1953, complaining mainly of pain in the lower part of the back, which seemed to radiate into both groins. She also had had a few brief episodes of pain and stiffness of the neck, and occasionally she had had stiff hands on awakening in the morning. The salient features on physical examination were a slightly elevated blood pressure, arteriolar sclerosis of the retinal vessels, and Heberden's nodes.

She was seen again in 1955 for a recurrence of the chief complaint at the first visit. This time, in addition to the findings already mentioned, thickening of the palmar aponeuroses and their digital extensions was observed.

In 1956 she was seen again for a routine physical examination. Her blood pressure was higher than before. There was sclerosis of the retinal vessels. The left ventricle was slightly enlarged. The range of motion of the neck was slightly limited. There was a Dupuytren's contracture in the right hand, and a nodule had formed at the base of the third finger on the left. The skin was adherent to the underlying aponeurotic tissue and had the characteristic puckered appearance.

The palmar aponeurosis has been studied by many investigators since Dupuytren, who first established thickening and shortening of the digital extensions as the basis for the flexion of the fingers.[24] Langhans, cited by Kocher, was the first to describe the pathologic changes in detail.[46] The vascular strands of loose connective tissue that divide the aponeurosis in longitudinal bundles appeared to become wider and more numerous. The cellular hyperplasia occurred in several areas, and wherever it was most marked, the regular course of the fibers seemed to be interrupted. Ledderhose[47] distinguished three stages in this picture. In Stage 1 the hyperplastic process occurred fairly evenly through the entire aponeurosis; in Stage 2 it was more localized, forming nodules in the thickened aponeurosis, and in Stage 3 contracture was seen. McWilliams[57] spoke of a chronic hyperplastic inflammation with subsequent formation of scar tissue in the fascia and in the adjacent connective tissue and fatty subcutaneous tissue as well. He deduced that first the fascial plate became thickened and that later this thickening also involved the digital extensions and the delicate fibers that radiate into the cutis.

Iklé[38] interpreted the pathologic picture as that of a connective-tissue neoplasm. There was a general hyperplasia of fibers and cells. Nodules were seen with a highly cellular periphery, sending extensions into the normal tissue. Occasional clumps of iron-containing pigment were also observed as well as rare perivascular lymphocytic infiltrations. Myerding et al.[58] were of the opinion that the main feature was proliferation of fibroblasts without other signs of inflammation, such as proliferation of capillaries and perivascular cellular infiltration. In the skin, the subcutaneous tissue, and the interstitial tissue such signs of inflammation could be seen, however. Horwitz,[37] too, believed the process to be one of a benign local fibroma. He noticed thickening of the palmar aponeurosis with advancing age and connected this with the greater frequency of Dupuytren's contracture in older age groups. He also believed, like Ledderhose, that various stages occurred and that transition from a relatively smooth hyperplastic stage to one of nodule formation and contraction could occur but that frequently the process remained at Stage 1 or 2 without progression to Stage 3. Clay[15] agreed with Horwitz, Myerding, and Iklé that there were areas that could be called a cellular fibroma, but he also observed fascias that had the same appearance as the internodular areas in others.

Skoog's description[81] agreed for the greater part with these authors. He described nodules and masses of fibrous tissue. The nodules were formed by areas of cellular hyperplasia. This proliferating fibrous tissue appeared to split the collagen bundles

of the aponeurosis. At other times it gave the impression of having ruptured the fibers. The new undifferentiated connective tissue appeared to issue from the perivascular tissue of adjacent vessels. Iron-containing pigment was found but only in the areas of proliferating fibrous tissue. The cords resembled tendons and looked very much like normal aponeurotic tissue but generally less cellular, owing to a relative increase of the intercellular tissue. Skoog deduced from his observations that Dupuytren's contracture resulted from the formation of scar tissue that was formed because of the production of small ruptures in the collagen bundles. This scar tissue would be responsible for the formation of nodules and contractures. He believed that trauma was responsible for these ruptures. Riniker [72] did not find microscopic ruptures and pigment deposits. He believed that the nodules were formed through fibroplasia. This was observed to occur around small areas of necrosis, rather than traumatic rupture.

This review of pathologic studies substantiates the clinical impression that Dupuytren's contracture is the final stage of a process of fibrous hyperplasia of the palmar aponeurosis.

Study of a Group of Patients with Hyperplasia of the Palmar Aponeurosis

Eighty-nine patients with hyperplasia of the palmar aponeurosis (HPA) were studied. They were selected as they were encountered in the arthritis clinic of the Rochester General Hospital, as well as in a private practice, which also emphasizes rheumatic diseases. In an attempt to circumvent this bias, 89 patients who did not have hyperplasia of the palmar aponeurosis were selected and studied in the same manner as the first group. This second group will be called the NHPA group. Each case was analyzed with a view to past and present symptoms and signs, age, and sex. The Ledderhose classification was followed in grouping the various stages of HPA. HPA without nodules or contracture was called Stage 1. In Stage 2 nodules could be palpated, and in Stage 3 actual contraction was present. In Stage 2 the skin of the hand palm was frequently adherent and "puckered"; in Stage 3 that was almost always so. Of the 89 HPA patients, 59 were in Stage 1; 25, in Stage 2, and 5, in Stage 3. The division as to sex was as in Table 1. The age spread is shown in Table 2.

The two groups appear to be comparable except for a somewhat larger number of patients in the fourth and fifth decade in the NHPA group.

It confirms the frequently made observation of greater incidence of HPA in the older age groups.

Past and present diseases and syndromes are compiled in Table 3. It is obvious that the only striking difference between the groups is the three times higher incidence of rheumatoid arthritis in the NHPA group.

All patients had evidence of localized conditions, such as degenerative arthritis bursitis, periarthritis. Analysis of this group made it necessary to consider the relative accuracy of diagnosis. As the patients were picked before it was known what course this study was going to take, not all the roentgenographic evidence that one might desire was secured. On the other hand, it is well known that minor degenerative changes occur in articular cartilage that cannot be found on physical examination and do not produce symptoms. This is degenerative

TABLE 1.—*Division as to Sex*

Sex	HPA	NHPA
Male	25	37
Female	63	52

TABLE 2.—*Age Spread*

Decade	HPA	NHPA
1	0	0
2	1	2
3	4	2
4	5	14
5	12	18
6	30	24
7	28	20
8	8	9
9	1	0

TABLE 3.—*Past and Present Disease Syndromes*

	HPA	NHPA
Diseases and syndromes		
Pulmonary tuberculosis	3	0
Pulmonary abscess	1	0
Pleural effusion (etiology unknown)	1	0
Pulmonary emphysema	0	1
Bronchial asthma	2	0
Myocardial infarct	3	2
Angina pectoris	2	0
Intraventricular conduction defect	1	1
Aortic valve disease	10	8
Mitral valve disease	2	2
Atrial fibrillation	0	3
Hypertension (etiology unknown)	8	8
Arteriosclerosis	?	?
Peptic ulcer	2	4
Hepatic cirrhosis	1	1
Amebiasis	1	0
Ulcerative colitis	0	1
Carcinoma breast	2	1
Syphilis	0	1
Pernicious anemia	0	1
Peroneal paralysis (etiology unknown)	0	1
Hypothyroidism	0	2
Hyperthyroidism	0	2
Colloid goiter	0	1
Diabetes mellitus	3	2
Rheumatoid arthritis	10	31
Disseminated lupus	0	1
Rheumatoid spondylitis	2	3
Rheumatic fever	0	1
Gouty arthritis	2	3
Senile osteoporosis	1	5
Spondylolisthesis (lumbar)	2	1
Osteoarthritis, periarthrosis, bursitis, etc.	Further analyzed	
Surgical procedures		
Pelvic surgery	14	13
Appendectomy	13	10
Mastectomy	2	1
Cholecystectomy	3	0
Intestinal Surgery	2	1
Herniorrhaphy	4	1
T & A	35	37

arthritis in an early stage. Furthermore, although gout and rheumatoid arthritis are systemic diseases with well-known characteristics, joints affected by these diseases not infrequently also show "degenerative" changes. These may be secondary to gout or rheumatoid disease, or gouty or rheumatoid arthritis may be superimposed on degenerative arthritis. Similarly, scapulohumeral periarthrosis may occure in connection with rheumatoid arthritis but is seen with at least the same frequency unrelated to that disease. The same may be said of epicondylitis and various types of bursitis.

Although it has been stated recently that involvement of the metacarpophalangeal joints always is due to rheumatoid arthritis,[50] observations made during the course of this investigation do not agree with that. A metacarpophalangeal joint may swell and become red and warm when the adjacent digital extension of the aponeurosis progresses from Stage 1 hyperplasia to Stage 2 or 3. This may occur when other signs and symptoms necessary for a diagnosis of rheumatoid arthritis are absent. Gout also may affect these joints.

As far as the spine is concerned, accurate diagnosis is not always possible either. It is well known that osteophytes, considered to be characteristic of degenerative arthritis, may be observed on the x-ray film in cases where the patient as well as the examining physician were totally unaware of their existence. On the other hand, pain in the neck or back may occur without clinically identifiable cause. However, both Collins [17] and Coventry et al.[21] have demonstrated that degeneration of the intervertebral disks may lead to the formation of osteophytes (the so-called "spurring"). Bick [8] believes that lesions involving the attachment of paravertebral ligaments to the vertebral bodies and intervertebral disks are responsible for this phenomenon. These observations allow us to postulate a defective mechanism due to lesions that have not provoked osteophyte formation.

This hypothesis is supported by the well-known fact that pain is frequently associated with abnormal curves (scolioses, loss or exaggeration of normal curves, etc.), also known to be precursors of degenerative arthritis.

Study of the brachialgia frequently associated with arthritis of the cervical spine has brought out additional support for this hypothesis. Usually brachialgia associated with spinal osteoarthritis is attributed to pressure exerted on the nerve roots by the osteophytes encroaching on the intervertebral foramina. This, however, is not necessarily so. Nathan [62] has pointed out that neuralgic pains in the limbs are observed in the early stages of ankylosing spondylitis before ankylosis occurs. Garrod [29] found that nerve-root symptoms in ankylosing spondylitis are not necessarily due to narrowing of the intervertebral foramina. These situations are probably analogous to the sequence of events in osteoarthritis. Buckley [13] stated that nerve-root symptoms may appear long before there is roentgenographic evidence of

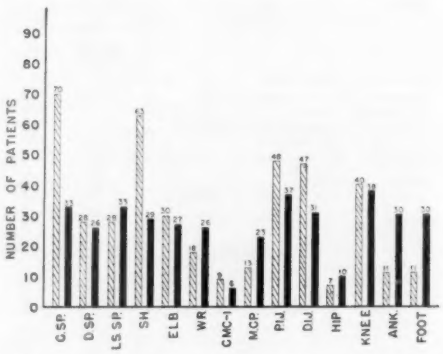
osteophyte formation. He also found that in the presence of unilateral osteophytosis the nerve-root symptoms may be on the contralateral side. This observation has been substantiated.[7]

Another observation [28] has shown that nerve roots may be stimulated more indirectly. Narrowing of the intervertebral disks shortens the cervical spine relative to the spinal cord. This tends to displace the nerve roots caudally in the foramina, so that they may be compressed against the edge of an intervertebral foramen which itself is not narrowed. Such a mechanism almost certainly is operative in abnormal curves, which in themselves are precursors of osteoarthritis, as pointed out above, or in congenital anomalies, such as block vertebrae or cervical ribs.

These observations undoubtedly may be applied to dorsal and lumbar spine as well. They make it possible and desirable to gather the disturbances of the spine that involve the disks, the vertebrae, and the relationship of the spine to spinal cord and nerve roots under the name of spondylosis.[11]

Instead of correlating HPA with systemic or local diseases involving joints, it was correlated with the conventional signs and symptoms of active joint disease. Repeated attacks of pain associated with limitation of motion were considered valid evidence for spondylosis, together with more obvious signs and symptoms.

Table 4 is a compilation of diseases of various sections of the spine and the peripheral joints as found in the HPA and the NHPA groups. The bar graph (Figure) illustrates the same data. Disease of the cervical spine and of the shoulder joint occur with a significantly greater frequency in the HPA than in the NHPA group. This finding appears to corroborate Steinbrocker's concept of the abortive shoulder-hand syndrome [86] and that of Coste's sympathosis.[19]



The abscissa indicates the three main portions of the spine and the peripheral joints. The hatched columns belong to the HPA, the solid black columns, to the NHPA group. The abbreviations are to be read as follows: C. SP. indicates cervical spine; D. SP., dorsal spine; LS. SP., lumbosacral spine; SH., shoulder joint; ELB., elbow joint; WR., wrist; CMC-1, first carpometacarpal joint; M. C. P., metacarpophalangeal joints; P. I. J., proximal interphalangeal joints; D. I. J., distal interphalangeal joints; ANK., ankle. Each indication belongs to a pair of bars.

This would indicate that HPA may be the result of a reflex or of a direct influence on the sympathetic effector fibers.

The neural mechanism of a reflex dystrophy is only partially understood. It has been well described elsewhere.[27,56] It may be sufficient to say here that it involves a reflex arc of sensory neurons and of effector neurons that may belong to the sympathetic nervous system. Between afferent and efferent neurons, internuncial neurons are interposed. They are supposed to spread the incoming stimuli to lower as well as higher levels, probably as high as the thalamus. It is believed that circular pathways may arise in this internuncial pool, along which incoming stimuli may be perpetuated. Thus the efferent neurons continue to be stimulated long after the original peripheral stimulus has ceased. Cervical spondylosis may influ-

TABLE 4.—*Diseases of Spine and Peripheral Joints*

	HPA	NHPA
Cervical spine	70	33
Dorsal spine	28	26
Lumbosacral spine	28	33
Shoulder	63	29
Elbow	30	27
Wrists	19	26
Carpometacarpal I	9	6
Metacarpophalangeals	13	23
Proximal interphalangeals	48	37
Distal interphalangeals	47	31
Hip	7	10
Knee	40	38
Ankle	11	30
Foot	11	30

ence the neural mechanism in two ways: (1) by irritating the afferent fibers and (2) by irritating the efferent fibers as they pass through the intervertebral foramina.

Much of what appeared to be controversial in the literature now can be approached in a more understandable manner. It is well known that trauma involving the upper extremity and the neck and myocardial infarcts may be stimuli followed by reflex dystrophy. Interruption of the reflex arc by blocking the stellate ganglion may be followed by improvement. Injury and disease of the peripheral and central nervous system may involve the reflex arc more directly. The reports of injury of the peripheral nerves preceding the appearance of a Dupuytren's contracture mention the ulnar nerve with striking frequency. This may well be due to the fact that "the upper extremity is provided with a relatively rich network of sympathetic communications," [86] especially from the outflow of the foramen between C_7 and D_1,[87] which forms the ulnar nerve. It also explains why reflex dystrophy occurs more frequently in the upper than in the lower extremities. Lead and barbiturates affect the nervous system directly. The thalamus is particularly influenced by barbiturates, and it should be remembered that the internuncial pool is supposed to reach as high a level as the thalamus. The higher frequency of HPA in the older age groups may well be connected with the greater frequency of cervical spondylosis in these age groups.

Even when one recognizes that a neural mechanism is involved, it is inconceivable to exclude other factors. Thus metabolic conditions have to be considered. Advancing age may alter the physicochemical mechanism of fibroplasia. Hepatic dysfunction, too, although not evident in this study, may create metabolic disturbances conducive to the development of HPA or to its progression from Stage 1 to further advanced stages.

The following case illustrates the causal relationship between cervical spondylosis and HPA.

CASE 2.—A 16-year-old boy was first seen in August, 1954, for the purpose of a general physical examination. Except for a tonsillectomy and adenoidectomy at the age of 3 and common diseases of childhood, his history was entirely unremarkable. The physical examination, urinalysis, blood cell count, and sedimentation rate were also well within normal range.

In October, 1954, he was seen again because he had awakened in the morning with severe pain in the neck and inability to turn his head. There was no evidence of systemic disease. Roentgenologic examination of the cervical spine showed a scoliosis, which was attributed by the roentgenologist to muscular spasm. Under suitable therapy he overcame this episode in five to six days. He experienced no further difficulty.

In June, 1956, he received another complete physical examination. This time there was Stage 1 hyperplasia of the palmar aponeurosis and slight enlargement of proximal and distal interphalangeal joints of the left hand.

This case brings up the question whether enlargement of the interphalangeal joints also belongs to the shoulder-hand syndrome. Stecher et al. have stated that Heberden's nodes develop only in the presence of a normal nerve supply to the hand. They, as well as Steinberg,[85] have observed the recession of Heberden's nodes in patients who became hemiplegic following a cerebrovascular accident. This may indicate that there is a neural component in the etiology of Heberden's nodes. On the other hand, the observed recession may be due to the same process that produces atrophy in denervated extremities.

Nothing is known about the etiology of degenerative arthritis of the proximal interphalangeal joints. There were 48 patients with disease of the proximal interphalangeal joints in the HPA group, compared to 37 in the NHPA group. It may be remembered that there were 31 patients with rheumatoid arthritis in the later group and only 10 in the former. There is a good chance that the difference between the two groups with reference to pure degenerative arthritis of the proximal interphalangeal joints is greater than the figures indicate. Further

investigation of the possibility of a neurogenic etiology of degenerative arthritis of the interphalangeal joints seems desirable.

This study also shows some evidence of the peculiar relationship between the scapulohumeral joint and the hand. Although it is evident that HPA is not a feature of rheumatoid arthritis per se, in those 10 cases in which it did occur there was involvement of the scapulohumeral joint as well. The topography of these cases was different in other respects.

The following case is offered as an example of the discovery of the existence of asymptomatic disease of the cervical spine following the observation of HPA.

CASE 3.—A 65-year-old woman was seen in September, 1956. Her presenting complaint was a pain described as reaching from the fingertips of the right hand, upward to the right shoulder. She had had limitation of motion of the right arm for four months. She was a diabetic who, taking 40 units of a long-acting insulin daily, had occasional insulin reactions. She had had a cholecystectomy, and bowel surgery of an unspecified nature had been performed many years ago. The salient points of the physical examination were bilateral hyperplasia of the palmar aponeurosis, Stage 2, with puckering and adherence of the overlying skin and swelling of the third right metacarpophalangeal joint, with a nodule in the third digital extension of the palmar aponeurosis adjacent to this joint. Pain was elicited by pressure over the anterior aspect of the right lateral humeral epicondyle. Abduction at the right scapulohumeral joint was possible only over a range of 45 degrees; rotation was not possible.

This patient repeatedly denied ever having had any pain or stiffness of the neck. In view of the experience with the HPA group discussed in this paper, roentgenographic studies of the cervical spine were made. They showed narrowing of several intervertebral spaces and osteophytes, encroaching on the intervertebral foramina.

One can only speculate about the reason for progression of early HPA to more advanced stages. Metabolic factors may be involved. The shoulder-hand relationship may also offer a clue. It is well known that the acute phase of scapulohumeral periarthrosis frequently follows trauma or strenuous motion, such as "overhead" work or the repetitious motions of painters or of switchboard operators. After the acute phase x-ray examination demonstrates the presence of calcific densities in the periarticular tissues. This may indicate that this process is associated with tissue necrosis.[2] In connection with this, it may be remembered that Riniker [72] recently stated that necrosis in the palmar aponeurosis was the inciting moment for the formation of nodules and contractures. The existence of a common mechanism, possibly neurogenic, that may produce tissue necrosis, should be considered.

Summary

Evidence is presented that supports Steinbrocker's concept of the "abortive" shoulder-hand syndrome. Hyperplasia of the palmar aponeurosis is not rare. It is the early stage of a Dupuytren's contracture. It may represent a neurogenic tissue change. A hypothesis concerning the progression of Stage 1 to Stage 2 or 3 is presented. The possibility of a neural factor in the etiology of degenerative arthritis of the interphalangeal joints should be investigated.

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The Relationship of Hyperthyroidism and Parkinsonism

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The simultaneous occurrence of Parkinsonism and hyperthyroidism in the same patient is an interesting relationship and one that presents problems of diagnostic and therapeutic importance. Several such cases have been cited in European literature and were offered as proof of the diencephalopituitary origin of primary hyperthyroidism.[6,9]

The essential pathology in Parkinsonism is a degeneration of the projection fiber system of the globus pallidus, with some changes of a milder degree in the substantia nigra.[8] These areas, located deep in the cerebral hemispheres, are immediately adjacent to the diencephalic areas of the brain. The diencephalon includes the thalamus, subthalamus, epithalamus, and hypothalamus, which, in turn, includes the neurohypophysis. The neurohypophysis, in combination with the adenohypophysis, forms the pituitary gland.

It seems apparent, then, that a disease process in either one of these areas might well affect both, owing to the proximity of their boundaries. Since most endocrinologists agree as to the diencephalopituitary origin of Graves' disease, it is feasible to postulate that a pathologic process, such as Parkinson's disease, located deep in the midbrain might somehow bring about changes of an irritative character in the immediately adjacent diencephalon, which in turn would precipitate Graves' disease.

In 1932, Alajouanine et al. reported a case in which both diseases developed during an episode of encephalitis. In 1939, Petit-Dutaillis performed a thyroidectomy on a patient with postencephalitic Parkinsonism and exophthalmic goiter, with resulting disappearance of symptoms of thyrotoxicosis with no effect on the Parkinsonism. In 1948, Paufique and Guinet[9] reported a 61-year-old man with left hemi-Parkinsonism, malignant exophthalmos, and a basal metabolic rate of +79%. This case was offered as evidence for the central origin of Basedow's disease. The authors suggested that the elevation of the basal metabolic rate in this patient was not mediated by the thyroid, presumably because there was no palpable goiter. The aforementioned authors supported Mahaux[7] regarding the suggested evidence for the central pathogenesis of Graves' disease.

For some time many authors (Moebius, Parhon, Gordon, Goldstein, Briese, Guillain, and Marquezy) have discussed the coexistence of hyperthyroidism and Parkinsonism, but there had been only rare observations as distinct as the case reported by Geraud and Gleize, in 1952.[6] These authors presented a 47-year-old woman in whom there occurred the clear-cut parallel evolution of exophthalmic goiter and Parkinsonism approximately 10 months after an episode of acute encephalitis. The patient had a basal metabolic rate of +30% and a 48-hour radioactive-iodine (I^{131}) uptake of 65%. She was treated with propylthiouracil and ethopropazine (Parsidol), trihexyphenidyl (Artane), and belladonna, with resulting clinical improvement and a basal metabolic rate of +18%. This case was presented primarily to confirm the diencephalopituitary origin of primary hyperthyroidism.

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It would appear from our observations that the simultaneous occurrence of hyperthyroidism and Parkinsonism is infrequent. An average of 300 new cases of hyperthyroidism are seen at the Lahey Clinic each year, and during the past decade we have been able to find only 12 cases of hyperthyroidism with associated Parkinsonism. This suggests that the association occurs about once in every 270 cases of hyperthyroidism. Should hyperthyroidism be seriously considered in every case of Parkinsonism that is seen, perhaps statistics would prove this relationship to be much commoner.

Clinical Manifestations

There are two main problems involved in the diagnosis of hyperthyroidism and Parkinsonism. The first is the detection of Graves' disease in a patient with known Parkinsonism, which occurs chiefly in the older patient with insignificant or no thyroid enlargement. The second problem is the decision as to whether an existing adenomatous goiter in a patient with known Parkinsonism is producing hyperthyroidism.

Problems related to the treatment of these two diseases are also involved. In the first place, the patient with Parkinson's disease may suffer rapid deterioration and even untimely death if the primary hyperthyroidism is not detected. Under such circumstances, merely treating the Parkinsonism is ineffective. The second problem is obvious. If an elderly patient with Parkinsonism has an adenomatous goiter, the decision as to whether or not this goiter is to be surgically removed may rest entirely on the presence or absence of hyperthyroidism. Therefore, an accurate diagnosis must be carefully established.

Well-established forms of either of these two diseases, existing separately, are usually easily distinguished. When they exist concurrently, the signs and symptoms of the Parkinsonism usually predominate, so that the identification of the hyperthyroidism may be difficult. Many of the symptoms and signs of hyperthyroidism are also present in patients who have Parkinsonism only. The following signs and symptoms are common to both diseases: (1) loss of weight, (2) loss of strength (apparent or real), (3) heat intolerance, (4) flushing of skin with increased sweating, (5) emotional lability, (6) widened palpebral fissures, (7) stare, (8) tachycardia, and (9) tremor.

The tremor which occurs in the two diseases is dissimilar. That of Parkinsonism tends to be coarse and irregular, varying in frequency from 3 to 10 per second, nonintentional, and of a resting type and may decrease during voluntary action. It usually disappears during sleep and increases in intensity with emotional excitement. The tremor of hyperthyroidism is rhythmical and so fine that it is more easily felt than seen. The tremor is intensified by holding the arms outstretched and spreading the extended fingers. This hyperthyroid type of tremor may be entirely masked by the coarse tremor of Parkinsonism.

Certain features of hyperthyroidism are not a part of the clinical picture of Parkinson's disease. If present, these may "break through" the predominant Parkinsonian features and provide the clinician with a clue to the presence of hyperthyroidism. These features are as follows: 1. Hyperorexia.[11] The marked increase in appetite observed in many patients with hyperthyroidism is absent in Parkinsonism. Anorexia, however, may be present in older patients with hyperthyroidism. 2. The characteristic fine, velvety smooth, warm, moist skin associated with hyperthyroidism is absent in Parkinsonism. 3. Thyrotoxic myopathy (muscle wasting of a severe degree) may occur in primary hyperthyroidism. Temporal muscle atrophy is manifested by a hollowing of the temporal fossae; deltoid, spinatus, interosseous, and quadriceps muscle atrophy may be present and can readily be demonstrated by appropriate tests of muscle strength. Rapid recovery of muscle mass follows adequate control of hyperthyroidism. In Parkinsonism, power of muscular contraction is retained to the end, as

tested by the patient's ability to resist an opposing movement. Voluntary movement nevertheless becomes slow and weak, owing to muscle rigidity. Thus, "paralysis" refers only to slowness of movement, not to the power of contraction of muscle.[3]

Laboratory Examinations

Several laboratory examinations may be helpful in establishing the diagnosis of hyperthyroidism in the presence of Parkinsonism.

Radioactive Iodine.—Twenty-four- and forty-eight-hour I^{131} uptake studies measure the avidity of the thyroid gland for iodine. Unfortunately, this test is not very informative in toxic adenomatous goiter, since it is known that this type of goiter can be overfunctioning without manifesting an increased uptake of I^{131}, and false-negative I^{131} uptake may result under certain circumstances. Also, false-positive results may occur in certain circumstances: (*a*) iodine starvation, (*b*) previous injection of thyroid-stimulating hormone, (*c*) increased circulating endogenous thyroid-stimulating hormone secondary to a low concentration of circulating thyroid hormone brought about by the use of antithyroid drugs. Chapman and Maloof[2] reported that "a normal thyroid may show an increased avidity for I^{131} after several months of antithyroid drugs." Increased uptakes have also been observed in some cases of renal disease.

Serum Protein-Bound Iodine.—Determination of the serum protein-bound iodine as a measure of the circulating thyroid hormone is a useful index of thyroid function. As in the radioactive iodine tracer studies, this, too, is subject to change by many factors other than hyperthyroidism.

Basal Metabolic Rate.—The difficulties that arise in the determination and interpretation of basal metabolic rates in various conditions are well known. The elevation of basal metabolism seen in such conditions as lymphoma, polycythemia, and congestive heart failure represents an actual increase in oxygen consumption under standard conditions of the test.[5] There may be no artificial element of tremor, fever, or lack of relaxation to give a result obtained under actual basal conditions.

On the other hand, the metabolic test carried out in the presence of such diseases as Parkinsonism, alcoholism, and various emotional states, although usually elevated, is rarely basal. Muscle tremor, rigidity, and lack of relaxation are factors contributing toward an erroneous end-result.

The abolition of Parkinsonian tremor with scopolamine to permit the demonstration of normal levels of metabolism has been suggested.[5] Total abolition of tremor is not always easily accomplished, however, as demonstrated by Doshay et al.[4] This group treated 520 patients with tremor and found that it completely disappeared in only 24, and of these, 19 were in the encephalitic group with tremors only incidental to the main problems of rigidity and oculogyric crises. Fifty-six of their cases, however, improved after treatment. Scopolamine and dyphenhydramine (Benadryl) were considered effective in relieving major and minor tremor, and trihexyphenidyl, stramonium, and phenindamine (Thephorin) were effective in instances of minor tremor only.

Of our 12 cases in which the hyperthyroidism was either proved absent or had been adequately treated and the Parkinsonian tremor minimized by medications, we were able to demonstrate a normal basal metabolic rate (taken under ordinary conditions in the standard postabsorptive state) in only 4.

A basal metabolism test carried out with use of sedation will eliminate the extraneous nervous factors that give rise to a false-positive result and permit the determination of a normal metabolic rate. The sedation in these cases consists of 0.1 gm. of pentobarbital (Nembutal) at bedtime on the evening before and 0.1 gm. again both on the morning of and one and one-half hours prior to the test.

In 3 of our 12 cases, in which the hyperthyroidism was ultimately controlled by antithyroid drugs, a basal metabolic test with use of sedation was carried out, and it was possible to demonstrate a normal basal metabolic rate in 2. In one case, sedation was ineffective and the presence of Parkinsonism continued to produce an elevated metabolic rate.

The basal metabolic test carried out with use of thiopental (Pentothal) anesthesia has served as our most practical final test in many cases of questionable hyperthyroidism at this clinic. This procedure induces a perfect basal state, void of all nervous and muscular factors. It has been found that in normal patients the metabolic rate drops an average of 8% with use of thiopental anesthesia and that an average of 0.5 gm. of thiopental is necessary to produce anesthesia. Hyperthyroid patients show little drop in the metabolic rate with use of anesthesia, and up to 2 gm. of thiopental is usually required to produce sleep.[1]

A basal metabolic test with use of anesthesia was accomplished in 3 of our 12 patients and was conclusive in all 3. The diagnosis of hyperthyroidism was proved in two patients and ruled out in the third.

In view of the comparative expense to the patient and of the unavailability of I^{131} in some areas, this test may well serve as a final decisive diagnostic measure in many cases.

Cases Studied

Our attention was first called to the relationship of hyperthyroidism associated with Parkinsonism as a result of several such cases that we have seen in the last few years. The interest thus generated led to a review of our files during the 1944 to 1955 period, with the disclosure of 12 patients in whom it had been necessary to evaluate the suspected presence of both Parkinsonism and hyperthyroidism. The problem in all of these 12 cases of Parkinsonism, therefore, became that of either establishing or disproving the presence of hyperthyroidism.

Summary of Cases

Case	Age & Sex	Diagnosis
1	62 F	Left hemi-Parkinsonism and adenomatous goiter (later proved to be nontoxic)
2	51 F	Idiopathic Parkinsonism and mild, recurrent primary hyperthyroidism
3	72 F	Arteriosclerotic Parkinsonism and recurrent primary hyperthyroidism
4	57 F	Idiopathic Parkinsonism and primary hyperthyroidism
5	69 F	Arteriosclerotic Parkinsonism and toxic adenomatous goiter (thyrocardiac)
6	62 F	Idiopathic Parkinsonism and severe primary hyperthyroidism
7	53 M	Postencephalitic Parkinsonism and toxic adenomatous goiter
8	43 F	Postencephalitic Parkinsonism and primary hyperthyroidism
9	38 F	Idiopathic Parkinsonism and primary hyperthyroidism
10	43 F	Idiopathic Parkinsonism and primary hyperthyroidism
11	58 M	Idiopathic Parkinsonism and primary hyperthyroidism
12	55 F	Idiopathic Parkinsonism and primary hyperthyroidism

A summary of our 12 cases is presented in the Table.

Four representative cases reveal the problem of diagnosis.

CASE 1.—A 62-year-old woman had been in good health until the age of 60, at which time a tremor of the left arm and hand developed. One year later, her family physician discovered that she had a goiter. The patient had always been a highly nervous person, had slept poorly, and often had sensations of warmth. Her appetite was poor, and there had been no weight loss. Three basal metabolic tests carried out at that time were said to have been +50, +60, and +95. It was assumed that the goiter was toxic, and the patient was treated with strong iodine (Lugol's) solution but without much benefit. She was then given antithyroid drugs, with appreciable improvement; she was less nervous, had an increase in appetite with a 5 lb. gain in weight, and had some decrease in tremor. She was later told that the basal metabolic rate was "normal."

Six months afterward, in January, 1950, the patient experienced an exacerbation of all symptoms; she was weak, fatigued, nervous, and had a marked increase in her tremor, which was, at the time, constantly present. There were no cardiovascular symptoms and no local obstructive symptoms due to goiter. She was first seen at the Lahey Clinic at this time. Her pulse rate was 84, and her blood pressure was 140 mm. systolic and 90 mm. diastolic. There was a marked tremor of the left arm, hand, and leg, with cogwheel rigidity demonstrable at the left elbow and wrist. A small (Grade I), palpable adenomatous goiter was present. Remaining physical findings were essentially negative.

It was initially believed that the goiter was nontoxic, but a routine metabolic test was +27.

A repeat test with use of thiopental anesthesia was then carried out, and her true basal metabolic rate was shown to be —4. Hyperthyroidism was thereby ruled out, and there was no need for surgical treatment. The final diagnosis was left hemi-Parkinsonism and nontoxic adenomatous goiter.

CASE 6.—A 62-year-old woman complained of tremor of one year's duration and nervousness, irritability, insomnia, polyphagia, and a 20 lb. weight loss of six months' duration. She had been aware of a swelling in the right side of her neck for six weeks. She also admitted intolerance to heat and palpitations. Her brother and father also had tremor involving the hands.

Physical examination revealed pulse rate 108 (regular, bounding in quality), blood pressure 130 mm. systolic and 70 mm. diastolic, and weight 118 lb. She was extremely agitated, with marked tremor (coarse and fine components) and a pill-rolling position of her fingers. The skin was warm and moist; eye stare, lid lag, and exophthalmos (Grade I) were noted. There was diffuse bilateral enlargement of the thyroid (Grade II).

Routine laboratory studies were noncontributory. Cholesterol was 181 mg. per 100 cc. An initial basal metabolic rate was +61. It was concluded that primary hyperthyroidism was present, and antithyroid drugs were given (propylthiouracil, 300 mg. per day for 66 days, with the addition of strong iodine solution during the last 15 days). Following this treatment, the coarse shaking and nervousness persisted, although the other symptoms had abated and she weighed 131 lb. A routine basal metabolic test was then +27; the pulse was 72, and blood pressure was 90 mm. systolic and 65 mm. diastolic. In view of her nervousness, the basal metabolic test was repeated with use of sedation and was +6. The patient was considered euthyroid, and a subtotal thyroidectomy was performed, with satisfactory postoperative recovery. The pathologic diagnosis was primary hyperplasia with moderate involution and hyperinvolution.

Follow-up basal metabolic tests three months to three years postoperatively ranged from +4 to —19 to —5. The only subsequent medication was phenobarbital, ¼ grain (16.25 mg.), as required, and the patient's tremor greatly diminished. The final diagnosis was idiopathic Parkinsonism and primary hyperthyroidism.

CASE 7.—A 53-year-old man came to the clinic with the chief complaint of tremor of one year's duration. An illness at the age of 16 was characterized by fever that persisted for 31 days and delirium. He was well until age 52, at which time there was gradual onset of a tremor of his right index finger. Several months later the tremor became generalized, involving both upper and lower extremities and his head. This persisted until the time of his first visit. He had taken caramiphen (Panparnit) for one month.

A goiter, present for 12 years, seemed to be increasing in size during the immediately preceding months. There had also been increased heat intolerance and sweating but no weight loss.

Physical examination revealed pulse rate 88; blood pressure 135 mm. systolic and 68 mm. diastolic; masked facies; coarse tremor of hands, legs, head, and tongue, decreasing with intention, and some cogwheel rigidity in neck and both arms. Otherwise neurologic tests were normal. The skin was warm and moist; he had a large nodular goiter, with gross firm enlargement of the right lobe of the thyroid and tracheal deviation to the left. The heart and lungs were normal.

Routine laboratory studies were noncontributory. Cholesterol was 117 mg. per 100 cc. Since the tremor was controlled by caramiphen, a metabolic test was carried out under ordinary conditions, and the metabolism was +17. It was concluded that the patient had a toxic adenomatous goiter.

The patient was treated with propylthiouracil, 300 mg. per day for 47 days. He became less nervous, gained 3½ lb., was more energetic, and slept well. A repeat basal metabolic test at that time was —9, with a pulse rate of 60 and a blood pressure of 125 mm. systolic and 70 mm. diastolic. Subtotal thyroidectomy was then done, and recovery was uneventful. The pathologic diagnosis was multiple colloid adenomatous goiter. Follow-up basal metabolic tests during the next two years ranged from —4 to +5. The Parkinsonism has remained under adequate control with medications. The final diagnosis was postencephalitic Parkinsonism and adenomatous goiter with secondary hyperthyroidism.

CASE 11.—A 58-year-old man had known Parkinsonism of four years' duration. A tremor of his right leg, arm, and tongue had developed gradually and progressed until January, 1955, at which time he was first seen at the Lahey Clinic. His pulse was 80, and blood pressure was 130 mm. systolic and 70 mm. diastolic; tremor (as described) and rigidity of right arm and leg were observed. Cycrimine (Pagitane) hydrochloride was selected for treatment.

By March, 1955, the patient became aware of the fact that he had lost 28 lb. in weight during the preceding eight months. His appetite was moderate to poor. The tremor had been considerably magnified during the preceding four months. Nervousness and emotional lability had become marked. Diarrhea had started shortly before this time. He also had heat intolerance and slept with feet out from under the bed covers.

Physical examination revealed pulse 108 at bed rest, blood pressure 200 mm. systolic and 100 mm. diastolic, masked Parkinsonian facies, marked

tremor of right arm and right leg, widened palpebral fissures and stare, warm moist skin, minimal gynecomastia of the right breast, marked cardiac thrust, and demonstrable quadriceps muscle weakness. The thyroid gland was palpable but within the limits of normal size.

It was obvious from the pronounced tremor and emotional lability that a basal metabolic test done under standard conditions would be of little value. Therefore, a metabolism test with use of thiopental anesthesia was done immediately, and the resulting basal metabolic rate was +38 and +32. I^{131}-uptake studies were carried out also, with a resulting uptake of 90%. The diagnosis of primary hyperthyroidism was thereby confirmed.

The patient was discharged from the hospital on April 20, 1955, with a regimen of propylthiouracil (500 mg. per day for 10 days, 250 mg. per day for 10 days, and 100 mg. per day for 3 weeks); stramonium, 2½ grains (0.187 gm.) twice a day; diphenhydramine, 25 mg. four times a day, and Cycrimine hydrochloride, 2.5 mg. four times a day. He quickly began to notice improvement in his condition, and by June, 1955, he was euthyroid. Pulse rate was 72; he had gained 16 lb. in weight; he had no heat intolerance; the legs were stronger on stairs; appetite had improved; tremor was less, and ability for self-care was improved. Cholesterol was 228 mg. per 100 cc. On June 15, 1955, he was treated with 7 mc. of I^{131}.

The final diagnosis was idiopathic Parkinsonism and primary hyperthyroidism.

Comment

Of interest in the association of the thyroid gland and Parkinson's disease is the recent work of Schwab and Chapman.[10] These workers used I^{131} in euthyroid patients with Parkinsonism to produce a hypothyroid state and obtained encouraging results. Objective evidence of clinical improvement was seen in six of nine selected patients. In the other three cases, although objective evidence of improvement was absent, the patients were improved subjectively.

Their criteria for treatment of Parkinsonian patients with I^{131} are (1) clinical evidence that the metabolic activity of the patient is in the upper range of normal, (2) the presence of dominant uncontrollable tremor, (3) a history of previous difficulty in maintaining body weight, and (4) evidence by tracer dose of I^{131} and protein-bound iodine studies that the thyroid function is in the upper range of or above normal. They thought it undesirable to depress further Parkinsonian patients who are in the low range of normal thyroid function or already hypothyroid.

These authors stated, "There is no evidence, of course, that lowering the thyroid function did anything more than make the Parkinsonism more tolerable to the individual." In the discussion that followed the initial presentation of that paper, however, it was apparent that some observers questioned whether or not the patients so treated had actually been relieved of symptoms of masked hyperthyroidism. In reply, Schwab revealed that only one of the nine patients had tracer and protein-bound iodine levels sufficiently high that, in retrospect, she would have been considered as having Parkinsonism and mild hyperthyroidism. All of the other patients had high-normal values.

This new approach in the treatment of Parkinsonism provokes considerable interest. Whatever relationship it has with the subject of this article remains for conjecture and further study.

Summary

The relationship of hyperthyroidism and Parkinsonism is discussed, principally with respect to pathogenesis, clinical picture, and diagnostic methods.

Twelve patients with associated Parkinsonism and hyperthyroidism are reviewed, and four representative case histories are presented.

The basal metabolic rate with use of anesthesia has served as a useful decisive diagnostic procedure in difficult cases.

Hyperthyroidism should be suspected in every case of Parkinsonism, since, if confirmed, treatment of the hyperthyroidism will lead to improvement in the Parkinson's disease.

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Thyroxin and Triiodothyronine in Excessive Dosage to Euthyroid Humans

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The comparative effects of 3,5,3′-*l*-triiodothyronine and *l*-thyroxin in myxedema have been carefully evaluated.[1] These medications have also been given in physiologic dosage to euthyroid humans to evaluate the effect on the thyroid I^{131} uptake and serum protein-bound iodine (PBI).[2] We have found no information on the comparative effects of "thyrotoxic" dosage of these drugs and the subsequent effect of stopping these medications.

In the course of an evaluation of the effects of induced thyrotoxicosis on mental function,[3] interesting new data were accumulated on this aspect of thyroid hormone effect.

Method

Subjects.—Eighteen healthy male college students ranging in age from 20 to 30 years—average age, 23 years—were screened by medical history, physical examination, 24-hour I^{131}-uptake test, basal metabolic rate (BMR), serum PBI,[4] and serum cholesterol[5] determination to rule out any question of thyroid disease and to make certain that they could withstand the effects of administration of excessive amounts of thyroid hormone. Six subjects were rejected, and twelve subjects served out the entire period of the experiment.

Experimental Plan.—Table 1 presents the data flow sheet.

Thyroxin * was given first to six subjects for 13 days in increasing doses in an effort to make them "thyrotoxic." Medication was then stopped abruptly, and the patients were allowed to recover from the effect of this medication for 11 to 12 days before starting triiodothyronine. Triiodothyronine was then given for 11 to 17 days in rapidly increasing doses to make the subjects "toxic." This medication in turn was stopped abruptly, and the patients were followed through a control period of 10 to 14 days. In the remaining six subjects triiodothyronine was given first, for 9 to 13 days, and thyroxin was given second, for 15 to 17 days.

Dosage.—Table 2 summarizes the total daily dosage of each medication given each day. Thyroxin total dosage was given in two equal doses at breakfast and bedtime. Triiodothyronine was given in three equal doses, t. i. d. The time intervals at which BMR, PBI, and cholesterol determinations were performed during medication and during recovery periods are presented in Table 1.

Results

BMR Response to Thyroxin.—Figure 1 summarizes the response of the BMR and serum cholesterol to thyroxin administration. With thyroxin therapy the mean BMR rose from −3.8% to +11.6% or 15 percentage points, by the time thyroxin was stopped. It is most interesting, and apparently not previously reported, that the BMR then continued to rise to +24% at 2 and 4 days after cessation of thyroxin administration and was still at a value of +10% at 10 days after cessation. In one subject, followed to 22 days after stopping thyroxin, the BMR was +7% at 14 days and −12% at 22 days.

BMR Response to Triiodothyronine.—The BMR and serum cholesterol response to triiodothyronine are summarized in Figure 2.

With triiodothyronine administration the mean BMR rose higher and maximum by the last day of medication. The maximum

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* Thyroxin was supplied by Travenol Laboratories, Inc., and triiodothyronine, by Smith, Kline & French Laboratories.

TABLE 1.—*Thyroid Function Studies*

Patient	Thyroid Hormone *	No. Days Administered	Base Line			Day During Administration: 4th			9th			Last		
			BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.
2	Th	13	−8	8.8	256				−1	12.0	248	+9	34.4	231
	Tr	17										+28	4.5	127
10	Th	13	−12	5.2	157							−8	16.4	123
	Tr	14										+19	3.3	98
9	Th	13	+6	4.7	246							+4	24.7	135
	Tr	11										+21	3.6	159
1	Th	13	−11	5.0	215				−3	17.5	210	+14	..	..
	Tr	17										+32	3.3	111
7	Th	13	−3	4.9	144							+18	17.7	104
	Tr	16									Last day	+1		
3	Th	13	−3	5.3	225				−10	14.6	234	+12	6.0	72
	Tr	17										+3	15.3	148
8	Tr	13	−17	6.1	217							+28	3.0	127
	Th	17										+13	4.7	163
4	Tr	9	−2	4.5	208							+34	16.3	137
	Th	17										+7	2.6	174
11	Tr	13	+2	3.5	185							+18	18.7	126
	Th	15										+13	2.5	126
												+21	17.0	114
													12th day	
5	Tr	13	+2	4.1	224				+1	2.4	239	+21	2.6	143
	Th	17										+2	20.8	148
12	Tr	13	−4	4.3	187							+14	1.7	111
	Th	15										+8	19.8	116
6	Tr	12	+4	5.1	236	−12	3.6	202	−3	2.8	195	+15	4.4	148
										13th day				
	Th	16							+1	26.9	154	+16	25.0	127

* Th indicates thyroxin; Tr., triiodothyronine.

TABLE 1.—*Thyroid Function Studies*—Continued

Patient	Day After Stopping Thyroid Medication																	
	2d			4th			6th			8th			10th			14th		
	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.	BMR, %	PBI, Mg./100 Cc.	Chol., Mg./100 Cc.
2							−6	6.3	184				+1	5.9	157			
10							−17	2.7	184				−3	3.9	237			
										?+14	5.5	102	−2	5.7	157			
9										−4	1.7	170	−14	2.2	160			
										+11	--	--	+7	8.4	185			
1	--	13.1	121				+11	7.9	132	−10	--	--	−15	2.3	209			
							+4	1.9	160				+9	5.9	141			
7													−9	2.4	208			
										?+34	12.3	97	+15	5.1	131			
3							+2	6.3	130	? −3	3.4	142	+14	2.2	137			
								7th day					+5	5.9	146			
8				+2	2.4	158	−19	3.1	175				−8	3.1	218			
													−2	2.8	270			
														11th day				
				+18	15.2	140												
4	+8	1.8	159										+18	8.5	169			
	+29	13.9	108										−17	4.4	218	−17	6.4	197
11				+27	3.3	124							+3	7.5	167			
	+18	16.3	111	+17	11.0	101							−5	3.1	214			
5	+3	1.9	136										+23	6.8	123			
	+27	15.3	140										−17	3.1	183			
12				−6	3.0	126							+15	5.5	157			
	+16	14.9	94	+28	14.2	106							−2	3.1	201			
6	+12	2.8	124	+6	2.0	188	−7	2.8	222				+11	5.8	111			
	+30	17.3	109	+33	12.5	109	+28	11.0	134	+13	8.5	136	−21	3.7	272			
													+13	6.7	145	+7	3.4	190
														22d day→		−12	4.5	233

TABLE 2.—*Dosage Schedule*

Day	Thyroxin, Mg./Day	Triiodothyronine, Mg./Day
1	0.2	0.050
2	0.3	0.075
3	0.4	0.100
4	0.5	0.125
5	0.6	0.150
6	0.8	0.200
7	1.0	0.250
8	1.2	0.300
9	1.4	0.350
10	1.6	0.400
11	1.8	0.450
12	2.0	0.525
13	2.0	0.525
14	2.0	0.525
15	2.0	0.525
16	2.0	0.525
17	2.0	0.525

mean rise in BMR after triiodothyronine was not as great as the maximum rise after thyroxin, however. The mean BMR value had fallen to premedication control levels by the sixth day after triiodothyronine withdrawal.

Serum Cholesterol Response to Thyroxin. The mean serum cholesterol fell 71 mg. per 100 cc., or 34%, from the control premedication mean value during thyroxin administration. It continued to fall through the 8th day after thyroxin withdrawal but had started to rise by the 10th day. In one subject (Patient 6) the cholesterol had not returned to pretreatment levels at 14 days but had returned by the 22d day.

Serum Cholesterol Response to Triiodothyronine.—As with the BMR response, the cholesterol response to triiodothyronine differed from the response to thyroxin in that the mean serum cholesterol value showed a response of greater and maximum magnitude by the last day of medication. After cessation of triiodothyronine administration

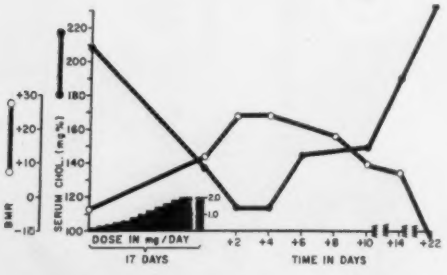

Fig. 1.—BMR and serum cholesterol response to thyroxin. Mean of 12 subjects.

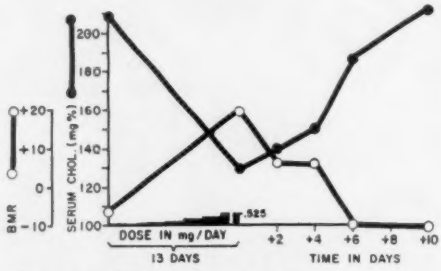

Fig. 2.—BMR and serum cholesterol response to triiodothyronine. Mean of 12 subjects.

there was no demonstrated lag period before the mean cholesterol value began to rise. The return to normal was completed in 10 days.

Serum Protein-Bound Iodine Response to Thyroxin.—Figure 3 compares the serum PBI response to thyroxin and triiodothyronine. The mean PBI value rose from 5.1 mg. per 100 cc. to 20.5 mg. per 100 cc. by the last day of thyroxin administration. Unlike the BMR and serum cholesterol the serum PBI had already begun to fall significantly within two days after thyroxin medication withdrawal and returned to premedication control values or below between the 10th and 14th days.

Serum Protein-Bound Iodine Response to Triiodothyronine.—The serum PBI response to triiodothyronine was opposite to the response to thyroxin. The mean serum PBI value fell during triiodothyronine medication from 5.1 to 3.6 mg. per 100 cc. and reached myxedema levels two days after

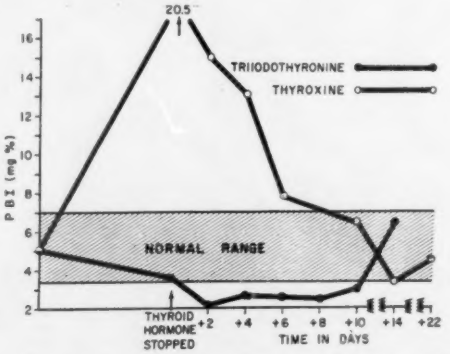

Fig. 3.—Serum PBI response to thyroxin and triiodothyronine.

triiodothyronine administration was stopped. The mean PBI values then stayed in the clearly subnormal range for 10 days but in the one subject followed longer than 10 days returned to premedication control value by 14 days after triiodothyronine withdrawal.

Serum Inorganic Iodine.—Serum inorganic iodine determinations were performed simultaneously with each PBI determination and showed no significant deviation.

Clinical Response.—Although most symptoms and signs were mild, all subjects complained of something. Nine subjects reported unusual headache; seven, insomnia; four, weakness and energy loss; four, fatigue; five, nervousness and irritability; one each, joint pains, loss of appetite, decreased tolerance for frustration, and palpitation on exertion. Incidence of signs consisted of one subject displaying unusual flush and perspiration; two, weight loss, and eight, tachycardia (basal pulse at time of BMR over 90). No placebo controls were carried out.

Comment

We have found no reports in the literature of the evaluation of the effects of excessive dosage and subsequent withdrawal of sodium-*l*-thyroxin or triiodothyronine on the BMR, serum cholesterol, and serum PBI. McConahey and Owen recently [6] summarized the literature on the effect of these two thyroid hormones on the I^{131} uptake. Starr and Liebhold-Shueck [2] assayed the effect of these two thyroid hormones in slightly greater than maintenance doses on the I^{131} uptake and serum PBI before and on the last day of administration of these compounds. Riggs et al.[7] made a most comprehensive study on the effects of administration of excessive amounts of desiccated thyroid to euthyroid humans.

Our study adds the following new information.

1. The BMR continues to rise and the serum cholesterol continues to fall when administration of sodium-*l*-thyroxin in increasing dosage is stopped.

Riggs and co-workers [7] observed almost no lag in the rise of the BMR behind that of the serum PBI during increase in dosage of desiccated thyroid to euthyroid persons. With cessation of thyroid dosage, however, the serum iodine fell much more abruptly than did the basal metabolic rate, but these persons did not demonstrate a continued increase in BMR or fall in serum cholesterol. Whereas the serum PBI fell to a low point 3 weeks after withdrawal of thyroid, the basal metabolic rates did not reach their lowest postmedication values for 9 to 15 weeks. This lag in fall of BMR after fall in serum PBI has also been demonstrated after thyroidectomy and after discontinuance of thyroid medication in patients with myxedema.[8] This lag has been interpreted to mean that thyroid hormone tends to disappear from the serum before it disappears from the tissues.[7] Disproportionately high levels of serum protein-bound iodine have been observed in hypothyroid patients receiving *l*-thyroxin,[9] as compared to euthyroid levels of serum PBI under similar circumstance with desiccated thyroid administration.[8] The explanation of this phenomenon might be "that thyroxine itself is weakly, or not at all, calorigenically effective and that its presence in the circulation represents a reservoir of the thyroid hormone for transformation to triiodothyronine, the biologically active factor." [1] This hypothesis might be used to explain our observed results. That is, rapid increase in dosage of thyroxin obviously loaded the intravascular pool of protein-bound thyroxin (Fig. 3, showing the rise in PBI level). The body cells could remove the 5′ iodine atom from thyroxine, thus allowing entrance of the intracellular form of thyroid hormone, triiodothyronine, to exert its increasing calorigenic effect as the serum PBI (blood thyroxin concentration) fell. Figure 3 shows that the BMR can rise and the serum cholesterol can fall while the serum PBI is falling during triiodothyronine administration (see the effect of triiodothyronine on the serum PBI).

2. Contrary to the lag effect on BMR and serum cholesterol after withdrawal of thyroxin, the BMR and serum cholesterol response to withdrawal of triiodothyronine administration was prompt. This is in keeping with the observed difference in duration of "calorigenic action" of thyroxin (long), as compared to the relatively short effect of triiodothyronine [1] and further deamination products of thyroxin and triiodothyronine.[10]

3. The relative calorigenic potency of triiodothyronine versus thyroxin is maintained at excessive dosage levels in euthyroid subjects much the same as at lower dosage levels in hypothyroid persons.

Asper [11] has found that the equivalent dosage of desiccated thyroid, sodium-*l*-thyroxin, and triiodothyronine in maintaining a hypothyroid patient in a euthyroid state is 3 grains (194 mg.) = 0.3 mg. = 0.1 mg., respectively. He has also shown [11] that this dosage level of thyroid hormone produces maximum supression of pituitary thyroid-stimulating hormone (TSH) activity. Therefore, the administration of thyroid hormone in doses up to these levels, while adding exogenous thyroid hormone to the body, should shut off pituitary TSH-induced endogenous secretion of thyroid hormone. Euthyroid persons do not become "hyperthyroid," therefore, until the dose of administered thyroid hormone exceeds normal endogenous thyroid hormone output quotas. As a matter of fact, subjects do not regularly become "hyperthyroid" until the dosage level of desiccated thyroid reaches 9 to 10 grains (582 to 648 mg.) per day.[7] The maximum dose of thyroxin given our subjects was 2.0 mg. per day for approximately six days. This is approximately seven times the dose necessary to produce maximum suppression of TSH. The maximum dosage of triiodothyronine was 0.525 mg., or 5.3 times the dose necessary to produce maximum supression of TSH. The BMR rose 28 points after thyroxin and 24 points after triiodothyronine, for a calorigenic ratio of 7:6. This compares closely with the figures of 7:5.3 TSH-suppression-dosage ratio given above.

4. Stabilization of the BMR and serum cholesterol has not been completed by 10 days after cessation of thyroxin and triiodothyronine. Our data suggest that stabilization may occur three weeks after triiodothyronine but not after cessation of dosage of thyroxin.

As stated above,[7] when desiccated thyroid administration to a euthyroid person is suddenly stopped, the serum PBI has been reported to fall to myxedematous levels in 3 to 4 weeks, and the lag in fall of the BMR may take 9 to 15 weeks to drop the BMR to its lowest level. Similarly, the thyroid 24-hour I^{131} uptake is depressed by desiccated thyroid administration. Although the majority of such persons have a return of such depressed I^{131} uptakes to normal in 2 weeks, in a few subjects the return to normal values may take as long as 6 to 11 weeks and then frequently rebound to hyperthyroid levels.[12] These phenomena occur presumably because as excess thyroid hormone is metabolized the body cell concentration of thyroid hormone must fall to low normal or subnormal levels before the pituitary is called upon to respond to this thyroid hormone deficiency by increasing its TSH output. The thyroid gland then responds to this renewed TSH stimulus. These reported abnormalities in thyroid function make it difficult for the practicing physician to decide how soon he can accurately assess thyroid function after a questionably hypothyroid person has been taken off thyroid medication. Our data suggest that thyroid function may normalize two to three weeks after triiodothyronine withdrawal, but more time must elapse after thyroxin withdrawal.

5. The administration of even excessive dosage of triiodothyronine results in a fall in serum PBI that continues downward after triiodothyronine withdrawal and remains in the myxedema range for more than 10 days. This drop in serum PBI presumably occurs because triiodothyronine action shuts off the endogenous supply of thyroid hormone by suppression of TSH

output but does not add to serum PBI directly because it enters body cells rapidly after having entered the blood stream. When the practicing physician is using the serum PBI to evaluate the thyroid status of a patient it is important for him to know that thyroxin administration elevates the serum PBI disproportionately to the patient's metabolic state and that triiodothyronine depresses the serum PBI during and for more than 10 days after administration. It is also interesting that after triiodothyronine withdrawal the pituitary-thyroid axis response does not become adequate to restore the intravascular pool concentration of thyroid hormone to normal range, as measured by the serum PBI, for over 10 days after the administration of triiodothyronine is stopped. Although the measurable calorigenic action of triiodothyronine usually lasts only five days, further degradation products of triiodothyronine [14] theoretically might continue to depress TSH output by the pituitary.

Summary and Conclusions

Thyroxin or triiodothyronine was given in excessive dosage (dosage large enough to elevate the basal metabolic rate [BMR] and depress the serum cholesterol) to 12 euthyroid healthy male college students. One drug was given first to six subjects, and the other drug was given first to the remaining six subjects. The drug was then stopped abruptly. The subjects were allowed to recover and then were given the second drug in excessive dosage. This drug in turn was abruptly discontinued, and the subjects were allowed to recover. The subjects were followed closely throughout the experiment, with BMR, serum cholesterol, and serum protein-bound-iodine (PBI) determinations. The following new observations were recorded and their significance discussed.

1. The BMR continues to rise and the serum cholesterol continues to fall for a few days after stopping administration of thyroxin in increasing excessive dosage.

2. This effect is not observed when administration of triiodothyronine in increasing excessive dosage is stopped.

3. The relative calorigenic potency of triiodothyronine versus thyroxin is maintained at excessive dosage levels in euthyroid subjects much the same as at lower dosage levels in hypothyroid persons.

4. Stabilization of the BMR and serum cholesterol was not complete 10 days after cessation of thyroxin or triiodothyronine.

5. The administration of even excessive doses of triiodothyronine results in a fall in serum PBI that continues downward after triiodothyronine withdrawal and remains in the myxedema range for more than 10 days.

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Disappearance of Electrical Alternans Following Pericardiocentesis

ALEXANDER F. GOLEY, M.D., and ROBERT SCHWARTZ, M.D., New Haven, Conn.

Electrical alternans is a regularly occurring variation in amplitude configuration, or direction of one or more of the components of the electrocardiogram. Those components which represent ventricular activity are most frequently involved, while P-wave alternation is unusual.[1,7,11,12,17] Alternation of the QRS and T complexes may occur alone or in combination with each other. This electrocardiographic abnormality is apparently rare. Hamburger, Katz, and Saphir[7] saw only one example of it in 10,000 electrocardiograms; Feldman[5] observed one instance in over 6000 electrocardiograms.

The following is a report of electrical alternans occurring in association with cardiac tamponade secondary to malignant involvement of the pericardium.

Report of a Case

A 34-year-old railroad worker was admitted to the Grace-New Haven Community Hospital on Jan. 22, 1957, because of an episode of syncope.

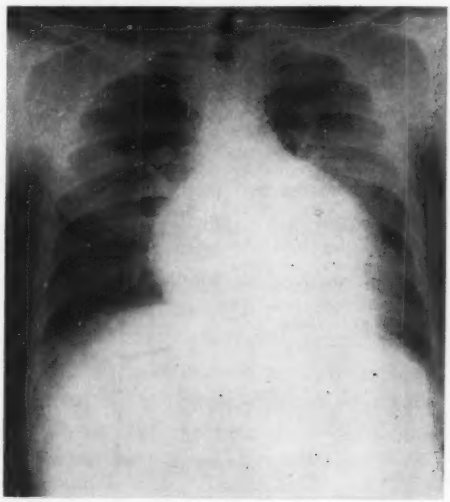
He was apparently well until three months prior to admission, when he consulted his physician because of a dull boring midepigastric distress which occurred about 10 minutes after meals. Radiologic examination was interpreted as showing a duodenal ulcer, and he was given a bland diet and antacids. This seemed to give some relief initially, but over the next three months he had increasing anorexia associated with a 22 lb. weight loss. During the three weeks prior to admission the epigastric pain became almost constant.

On the morning of admission he noticed weakness and marked dyspnea on exertion. Later in the day he fainted while at work. A physician found him to be pale and perspiring, with a rapid thready pulse. He was immediately admitted to the hospital.

His past history gave no evidence of tuberculosis or rheumatic heart disease. His family history revealed that his father and an older brother had each died of carcinoma of the stomach.

Physical examination revealed a pale wasted man in no acute distress. Temperature, 101 F (rectally); pulse, 120 per minute; respirations, 20 per minute; blood pressure, 110/80. There was no significant adenopathy. His chest was symmetrical, and lung fields were clear. His neck veins were not distended when his trunk was elevated at a 30-degree angle. The left border of cardiac dullness was at the anterior axillary line in the sixth intercostal space, while the point of maximal impulse was weak and 4 cm. medial to this. Heart sounds were distant, and no rub, gallop, or murmur was heard. The abdomen was scaphoid, with marked tenderness and guarding in the right upper quadrant. No abdominal mass could be palpated, and bowel sounds were normal. There was no peripheral edema. His total leukocyte count was 15,000 per cubic millimeter, and

Fig. 1.—Chest x-ray taken on the day of admission, showing pericardial effusion.



Submitted for publication June 17, 1957.

Intern in Medicine (Dr. Goley) and Assistant Resident in Medicine (Dr. Schwartz), Grace-New Haven Community Hospital.

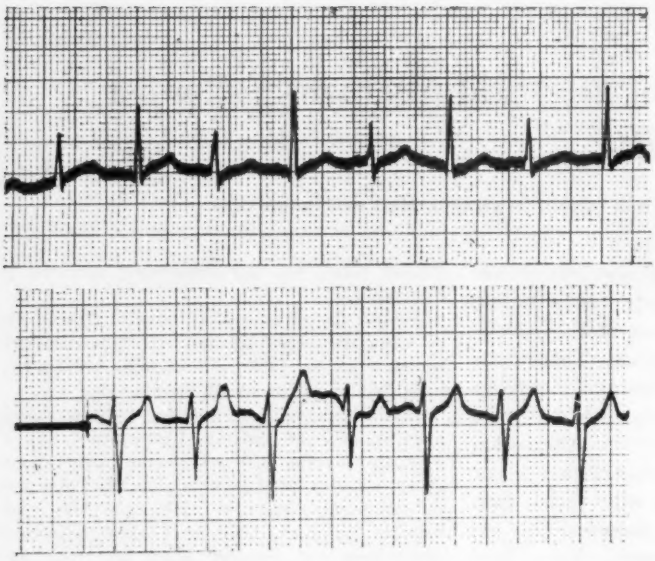


Fig. 2A.—Serial electrocardiograms, Leads V_5 and V_6. Electrocardiogram taken on admission, demonstrating alternation in amplitude of the QRS complexes. At that time venous pressure was 270 mm. of saline.

his hematocrit was 30 vol.%; urinalysis was normal, and stool was negative for occult blood. Transaminase was 8 units.

A chest x-ray (Fig. 1) was compatible with massive pericardial effusion, and a survey film of the abdomen revealed only hepatomegaly. Electrocardiogram demonstrated ST elevation in Leads II, III and aV_F. Marked alternans of the QRS complexes was seen in Leads I and VI through V_6. T and P waves were normal. Venous pressure was 270 mm. of saline; arm-to-tongue circulation time with dehydrocholic acid (Decholin) was 19 seconds. No pulsus alternans was noted.

During the next 24 hours the patient complained of increasing dyspnea. His neck veins became extremely distended, and his blood pressure fell to 95/70. Venous pressure at this time was 300

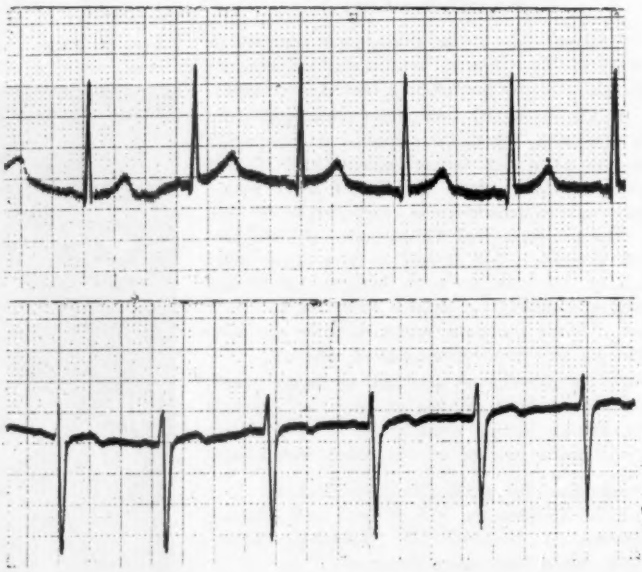


Fig. 2B.—Serial electrocardiogram, Leads V_5 and V_6. Electrocardiogram taken immediately after removal of 500 cc. of fluid from the pericardial sac. Venous pressure was 120 mm. of saline at the time this tracing was obtained. Note the disappearance of alternation and the increase in voltage.

Fig. 2C.—Serial electrocardiogram, Leads V_5 and V_6. Electrocardiogram taken four months after discharge, with normal complexes.

mm., and circulation time was 24 seconds. Because of this a pericardiocentesis was performed with use of the left paraxiphoid approach. Five hundred cubic centimeters of grossly bloody fluid was removed with marked relief of the patient's symptoms. An electrocardiogram taken during the procedure showed complete disappearance of the electrical alternans (Fig. 2). The venous pressure dropped to 120 mm. of saline and the circulation time fell to 13 seconds. Cell block done on the pericardial fluid was positive for tumor cells. It was necessary to repeat this procedure two days later. Again the patient's symptoms were relieved, and the electrical alternans which had reappeared was again obliterated.

Radiological examination revealed a huge ulcer crater along the greater curvature of the fundus and an hour-glass deformity of the stomach. A Wood's-tube biopsy was done, and this revealed adenocarcinoma.

Although the pericardial effusion persisted, the patient had no further symptoms of cardiac tamponade, and an electrocardiogram taken three months later failed to demonstrate electrical alternans.

Comment

Electrical alternans was first described by Mines,[14] in 1913, in a report concerned with the electrical activity of the frog's heart. Several years after this observation a number of articles concerning it appeared in the European literature. Poumailloux [16] wrote a monograph on the subject, which appeared in 1930. Hamburger, Katz, and Saphir [7] brought electrical alternans to the attention of American physicians in 1935 with their description of two examples. Since then electrical alternans has been reported in association with various tachycardias,[11,15] pericardial effusions,[5,12,13,18] the use of digitalis,[11,17] severe coronary artery disease,[2,7,8,11] cardiac metastases,[5,7,8] and severe heart failure.[2] The appearance of electrical alternans with tachycardia is said by most authors to have no clinical significance, but in the absence of marked tachycardia it carries a serious prognosis.

This abnormality must be differentiated from ventricular bigeminy, which is irregular by virtue of the premature beats, and from alternating bundle-branch block. Although bidirectional complexes are regarded

by most authors as electrical alternans, Bellet [1] does not accept this concept.

From the physiologic viewpoint there is probably only one form of cardiac alternation, which may be expressed by either mechanical or electrical variations. Mechanical alternans is clinically manifested by pulsus alternans, "alternation of the force of contraction without alternation of rhythm." [6] This may be palpable over arteries, visible over veins, or audible over the heart. Very slight degree of alternation may be discovered while taking the blood pressure. It has the same clinical significance as electrical alternans but usually occurs independently of it. In many instances pulsus alternans is precipitated by an extrasystole.[1,17] Mines [14] suggested that electrical alternans was due to lowered excitability of a portion of heart muscle. Carter and Stewart [3] found it to occur in association with fatigue of the myocardium of the terrapin. The present case demonstrates that cardiac compression by a pericardial effusion may be responsible for electrical alternans. McGregor and Baskind [12] had a similar experience with some of their cases of pericardial effusion. It has been postulated that interference with myocardial nutrition resulting from cardiac compression may be responsible [10]; however, McGregor and Baskind [13] have suggested that the movement of the heart within the fluid-filled pericardial sac plays an important role. They have suggested that electrical alternans be added to the list of electrocardiographic changes seen in association with pericardial effusion. They collected 26 cases of pericardial effusion, and in 9 of these electrical alternans was a prominent feature. Harvey and Whitehall [9] noted its presence "occasionally" in their series of tuberculous pericarditis. Falk and Ebert [4] studied 25 cases of tuberculous pericarditis, 18 of which had pericardial effusion; in none of these was electrical alternans described. In our patient there was a definite relationship between the degree of cardiac tamponade and the appearance of electrical alternans. This observation suggests that electrical alternans can be correlated more closely with the degree of cardiac compression rather than with the presence of a pericardial effusion per se.

Summary

A case of cardiac tamponade is described in which electrical alternans was observed. On the two occasions when the tamponade was relieved by pericardiocentesis the electrical alternans disappeared.

Dr. Robert Lowman helped in the management of this patient.

Grace-New Haven Community Hospital, 789 Howard Ave. (4).

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Movements and Forces of the Human Heart

IV. Precordial Movements (Kinetocardiograms) in Relation to Ejection and Filling of the Ventricles

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The present study is one in a series designed to elucidate the genesis of the precordial motions. It is concerned with an attempt to learn whether low-frequency precordial tracings (kinetocardiograms [KCG]) can be utilized as an index to the time of onset of ejection and filling.

A number of observers have published data concerning the time elapsing between the beginning of electrical excitation and the start of the pressure rise in the pulmonary artery and the aorta.[1-3] These studies indicate that the right and left ventricles begin to eject at approximately 0.08 and 0.10 second, respectively, after the onset of the QRS. Similar studies indicate that ventricular filling begins about 0.10 second after the beginning of the second heart sound.[2] Consequently, this study is concerned with precordial motions occurring at these particular times, in the hope that such events may afford information which can be readily and simply obtained and which will furnish a guide as to the time of onset of ejection and filling of the ventricles.

Methods

The subjects studied were 36 men who lacked evidence of cardiac disease. Of these, 25 were in the third decade; 6, in the fourth, and 5, in the sixth or seventh.

Records were made from various interspaces in the right and left parasternal regions, in the left midclavicular line, in the area of the apex, and also from the right and left epigastric regions. Two techniques were used for recording the precordial tracings. One of them was the crossbar-bellows method described in previous communications.[4-6] The other involved the use of a funnel 11 cm. in its largest circumference, which was strapped to the chest. In the center of the funnel was a small bellows, motion of which was activated by a metal probe 3 mm. in diameter, which was placed in an intercostal space at the desired point. The results obtained by the two procedures were similar except in regard to some minor details, which will be mentioned later.

As reference tracings, the electrocardiogram and the carotid pulse were utilized.

For convenience of description, the various precordial points are designated as follows: The letter K is used to denote the kinetocardiogram, and numerals are utilized to indicate the transverse and vertical positions—one meaning right parasternal, two meaning left parasternal, and four meaning left midclavicular. Thus the first, or left, numeral has the same significance as that in the V leads of the electrocardiogram. The second, or right, numeral refers to the interspace. Thus K_{13} represents the kinetocardiogram obtained from the third interspace in the right parasternal line; K_{45}, that obtained from the fifth interspace in the left midclavicular line, etc. The terms K_{ER}, K_{EL}, and K_X refer, respectively, to traces from the right and left epigastric regions and from the point of maximal impulse. Thus in stocky subjects with transverse hearts, the K_X point might correspond to K_{45} or even K_{44}, while in slender persons with vertical hearts the K_X point would tend to be K_{55} (i. e., the fifth interspace midway between the left midclavicular and the left parasternal lines).

Results

A. Events Apparently Related to Right Ventricular Ejection.—At 0.088±0.02 second after the beginning of the QRS complex, certain consistent motions were noted. These are summarized in the Table and are illustrated in the various figures. There was abrupt inward motion (downstroke) occurring at the K_{14} and K_{23} points (Fig. 1).

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From the Department of Medicine, Medical College of Alabama.

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Precordial Events Apparently Related to Right Ventricular Ejection
Seconds After Onset of QRS *

		Inward Movements				Outward Movements			
		K_{13}	K_{14}	K_{15}	K_{24}	K_{25}	K_x	K_{2a}	K_{2b}
Funnel method	Subjects studied, No.	12	25	12	12	12	15	25	25
	Movement present in	12	25	10	12	12	23	16	18
	Earliest	0.08	0.07	0.08	0.08	0.08	0.07	0.08	0.10
	Latest	0.10	0.11	0.11	0.11	0.10	0.10	0.10	0.12
	Average	0.088	0.090	0.089	0.089	0.090	0.088	0.088	0.108
Crossbar method	Subjects studied, No.	11	11	11	11	11	11	11	11
	Movement present in	10	11	10	7	10	7	0	7
	Earliest	0.07	0.07	0.07	0.06	0.08	0.07	--	0.10
	Latest	0.11	0.11	0.10	0.10	0.11	0.10	--	0.13
	Average	0.089	0.085	0.080	0.084	0.091	0.087	--	0.109

* K_{13} indicates 3d interspace; K_{14}, 4th interspace; K_{15}, 5th interspace; right parasternal line. K_{24}, 3d interspace; K_{25}, 5th interspace; K_x, point of maximal impulse, left parasternal line. K_{2a}, right epigastrium; K_{2b}, left epigastrium.

This was often the largest movement of the cardiac cycle. The K_{13} and K_{15} tracings, likewise, usually exhibited a downstroke synchronous with the K_{14} record (Fig. 2).

As the aforementioned areas displayed the onset of inward motion, other regions began to move outward. This was usually observed at the K_{25}, K_{26}, and K_x points (Table and Figs. 3 and 4). Records from the K_{24} area were somewhat variable, outward motion being more frequent than inward.

Traces recorded from the exact point of maximal apical impulse, as determined by palpation and checked by fluoroscopy, displayed a fairly consistent pattern (Fig. 4).

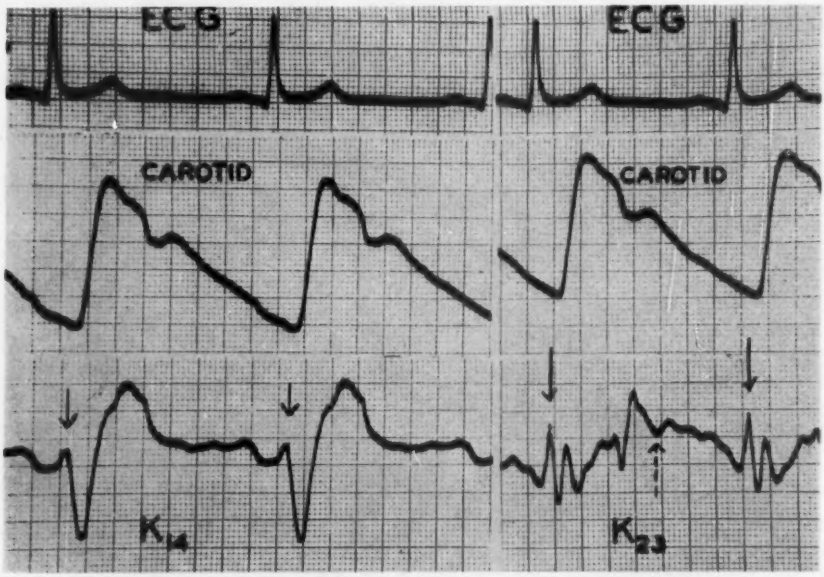

Fig. 1.—Precordial tracings by funnel method at K_{14} (right parasternal fourth intercostal space) and K_{2a} (left parasternal third intercostal space). The paper speed is 50 mm. per second. The sharp inward movement (solid arrow) at 0.09 second after the Q of the ECG is evident. This downstroke is approximately synchronous with rise in the pulmonary artery pressure and is apparently related to the volume change of right ventricular ejection as reflected at these points on the chest wall. The K_{2a} trace exhibits a large upstroke, starting slightly before the carotid incisural notch. This is ascribed to relaxation. A smaller upstroke (dotted arrow), beginning about 0.10 second after the incisura, indicates filling. In this subject the K_{14} record does not show a filling upstroke. During the latter part of the ejection period the K_{14} record is above the diastolic baseline. This is true, in less degree, of the K_{2a} trace. Thus large outward motion during ejection is not abnormal in these regions when the funnel technique is used.

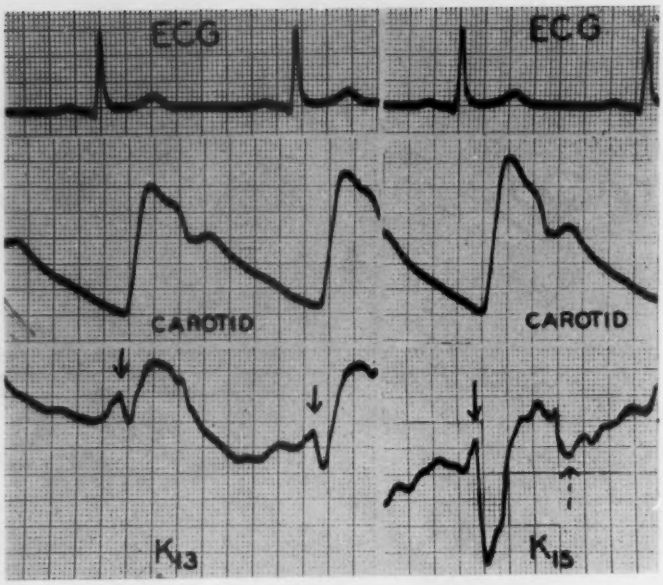

Fig. 2.—Same subject and paper speed as in Figure 1. Funnel method. Kinetocardiograms at K_{13} (right parasternal third intercostal space) and K_{15} (right parasternal fifth intercostal space). A sharp downstroke (solid arrow) synchronous with the previous (Fig. 1) tracings (K_{14} and K_{28}) is evident at 0.085±0.015 second after the beginning of ventricular excitation. The K_{15} downstroke is not always as evident as here. An upstroke (dotted arrow) beginning 0.08 second after the incisural notch and seen in the K_{15} but not in the K_{13} trace. The K_{13} record, which has a configuration similar to the carotid trace, is obviously much influenced by the movements of the underlying aorta. During most of systole it is above the diastolic baseline. Even the K_{15} trace is elevated above the baseline during the latter part of systole. Therefore, such elevation in these regions is not evidence of abnormality.

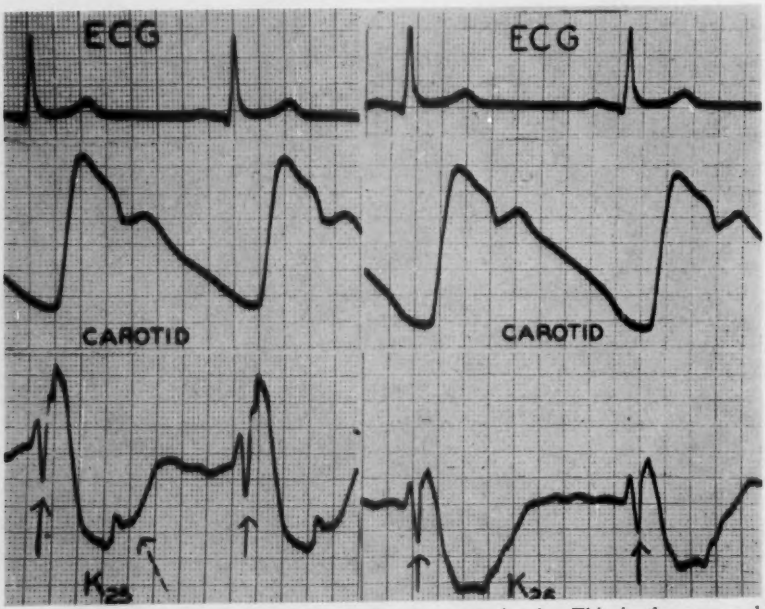

Fig. 3 (Left parasternal, fifth and sixth interspace tracings).—This is the same subject depicted in Figures 1 and 2. Paper speed, 50 mm. per second. Funnel method. Sharp outward movement (solid arrow), invariably was recorded in the left parasternal fifth interspace and usually in the sixth interspace at about 0.09 second after the onset of Q. This is apparently related to recoil of the right ventricle. The K_{25} trace displays two late upstrokes, the first (relaxation) beginning about 0.04 second before and the second (filling) starting about 0.05 second after the carotid incisural notch. In the K_{26} trace these two upstrokes are continuous and the forward movement of ventricular filling is not clearly defined. Comparison with Figures 1 and 2, from the same subject, indicates that the forward movement of filling (dotted arrow) occurs slightly earlier at the K_{25} area (0.44 second after the QRS onset) than at K_{28} (0.48 second) and K_{15} (0.47 second). These records, unlike those in the preceding figures, remain well below the diastolic baseline throughout the ejection period. Thus in the lower left parasternal region a midsystolic elevation above the baseline is evidence of abnormality.

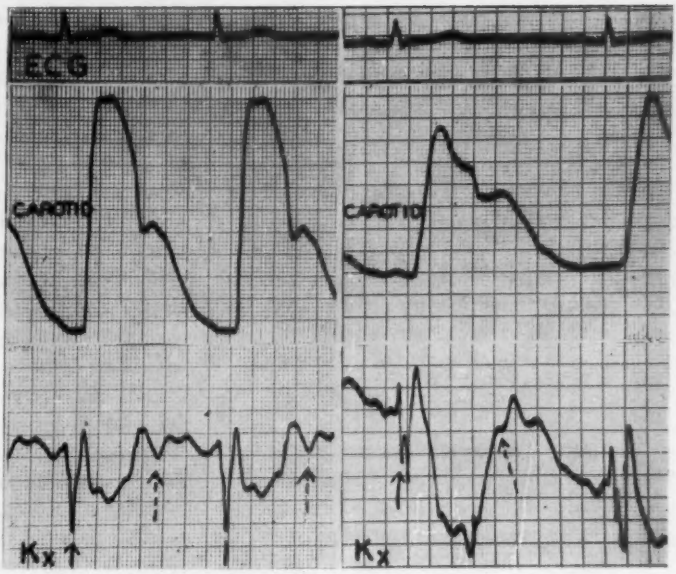

Fig. 4.—Paper speed, 50 mm. per second. Funnel method. Kinetocardiograms recorded from the exact point of maximal impulse, as determined by palpation and fluoroscopy, show a distinct and usually biphasic outward movement beginning at 0.085±0.015 second after the start of ventricular excitation (solid arrow). The onset of this motion is attributed to recoil as right ventricular ejection is initiated. The second portion of the biphasic apical outward movement begins at 0.105±0.015 second after the onset of ventricular excitation. It is ascribed to a second recoil as left ventricular ejection begins (text). Both subjects display two late forward motions (upstroke). The first of these, which begins at about the time the rapid downstroke of the carotid incisural descent starts, is attributed to relaxation. The second and smaller upstroke (dotted arrow) beginning 0.07 (left tracing) and 0.11 (right tracing) second after the incisural notch is ascribed to ventricular filling. Following the brief apex beat the apical trace from normal subjects remains below the diastolic baseline during ejection.

Fig. 5.—Paper speed, 50 mm. per second. Funnel method. Same patient as in right-hand tracing in Figure 4. The right epigastric trace (K_{ER}) displays a steep upstroke (arrow) superimposed on the previous gentle upstroke and beginning 0.07 second after the onset of the QRS. This movement, when present, corresponds in time to the upstroke in the left lower parasternal region and to the first part of the biphasic apical upstroke. It is ascribed to rightward footward recoil as the right ventricle ejects.

The left epigastric trace (K_{EL}) exhibits an upstroke (arrow) starting 0.11 second after the onset of the QRS. This movement corresponds in time to the second part of the biphasic apical upstroke. It is attributed to leftward footward recoil as the left ventricle ejects.

An outward movement was present, usually noted beginning 0.85±0.015 second after the onset of ventricular excitation.

Traces from precordial points other than those mentioned showed less tendency toward a consistent pattern. The right epigastric tracings (K_{ER}) often exhibited an upstroke beginning 0.085±0.015 second after the onset of the QRS (Fig. 5). This was observed in 16 subjects in this series and has been recorded in 52 normal subjects not included in this study. In about two-thirds of the subjects, the left epigastric (K_{EL}) region displayed an upstroke starting about 0.02 second later (Table).

Comment: The several events which have been described occur about 0.005 second after the time of onset of the pressure rise in the pulmonary artery, as found in catheterization studies.[1-3] It therefore appears likely that these various events are related to right ventricular ejection. Thus the sharp inward movement at the K_{13}, K_{14}, and K_{23} regions are ascribed to the volume change of ejection as the right ventricle moves inward. The sharp outward movement at the K_{25}, K_{26}, and K_{ER} area is ascribed to recoil of the heart as the right ventricle ejects. The variability in the records obtained from the lower right parasternal interspaces and from the K_{24} area probably indicates predominance of the inward movement of ejection and the outward movement of recoil in different subjects. It therefore appears that right ventricular ejection causes footward, forward, and rightward recoil of the heart. Since the recoil is in a footward direction, it is not usually observed in tracings taken over the upper portion of the right ventricle.

Records from the left midclavicular line displayed considerable variability. When the apex beat was exactly located by palpation and checked with fluoroscopy, a consistent pattern emerged. In most such traces a distinct and usually biphasic outward movement started 0.085±0.015 second after the Q of the ECG. Records were made an interspace above or below the apex and 1 cm. to right and left of it in seven normal subjects. These were generally similar but more variable than those made from the exact point of the apex.

Summary: At the time of right ventricular ejection the right parasternal and the upper left parasternal regions move inward, while the apical and lower left parasternal areas move outward.

B. Events Apparently Related to Left Ventricular Ejection.—In most normal subjects, the carotid upstroke begins 0.12±0.02 second after the onset of the QRS complex. The distance from the root of the aorta to the recording capsule in the neck is about 10 to 15 cm. If a pulse-wave velocity of 7 meters per second is assumed, then the time from the beginning of left ventricular ejection to the start of the carotid upstroke should be 0.015 to 0.02 second. Thus one arrives at a value of about 0.10 second for the onset of left ventricular ejection, and this is confirmed by data obtained by direct puncture or catheterization. These data indicate that the rise in the pressure at the root of the aorta in the human subject begins 0.10±0.015 second after the start of electrical excitation.[1] Hence any precordial reflections of left ventricular ejection would be expected to begin at about 0.10 second after the start of the QRS complex. Study of the precordial motions at this time yielded the following results.

At the parasternal areas, any movements related to left ventricular ejection were usually masked by the previous ejection of the right ventricle. However, in some subjects, and especially when the crossbar technique was used, the right parasternal records seemed to display evidence of the onset of left as well as of right ventricular ejection (Fig. 6). In the left epigastric traces (K_{EL}) two-thirds of the subjects showed outward motion, starting about 0.11 second after the beginning of the QRS (Fig. 5). This motion always followed the similar outward motion in the right epigastric (K_{ER}) traces by about 0.02 second in those subjects displaying both motions.

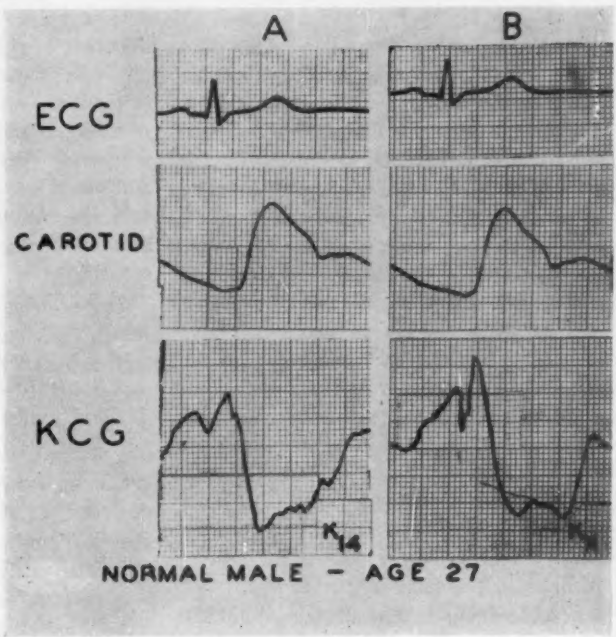

Fig. 6.—Crossbar method. Paper speed, 50 mm. per second. *A*, the main downstroke begins 0.075 second after the onset of the QRS. This is ascribed to right ventricular ejection. This downstroke is biphasic, the second portion starting 0.105 second after the onset of excitation and 0.02 second before the beginning of the abrupt carotid upstroke. The start of this second phase of the inward motion is believed to represent the initiation of left ventricular ejection. The outward motion (upstroke), starting 0.44 second after the onset of the QRS and 0.03 second after the carotid incisura, is attributed to ventricular filling. *B*, At 0.09 and 0.11 second after the start of the QRS there may be seen the two portions of a biphasic upstroke. These are ascribed to recoil of the right and left ventricles, respectively. The abrupt forward motion (upstroke), starting 0.04 second after the incisural notch and 0.45 second after the beginning of excitation, indicates ventricular filling.

Traces from the left anterior and midaxillary regions often showed a sharp upstroke at this time of the cycle. However, this movement was absent in some subjects.

Records obtained from the midclavicular line in the various interspaces exhibited considerable variability. However, traces obtained from the precise point of maximal impulse displayed the following findings: In all of the subjects in this group a distinct outward movement was recorded at 0.105± 0.015 second after the beginning of ventricular excitation. In most instances this represented a change in slope of the outward movement which began somewhat earlier (Fig. 4). This biphasic character of the apex thrust has been described in a previous report.[7]

Comment: Information related to left ventricular ejection as obtained with kinetocardiograms seems to be best recorded from the point of maximal precordial impulse and, less consistently, from the left axillary and left epigastric areas. Upstrokes (outward movements) in the regions starting about 0.105 second after the onset of excitation are attributed to recoil.

C. Events Apparently Related to Ventricular Filling.—At 0.47±0.05 second after the onset of the QRS and 0.06±0.04 second after the carotid incisural notch, outward movement of the precordium occurs. This is often earliest and best seen at the K_{25} and K_{26} areas (Fig. 3). It is commonly absent in the upper right parasternal (K_{13}) region but is often present at the other points (Figs. 1, 2, 3, 4, and 6).

Records obtained from the point of maximal impulse showed in all subjects outward precordial movement starting 0.48±0.05 second after the beginning of the QRS complex of the ECG. This movement should not be confused with the more abrupt and usually larger forward motion, which appears to be related to relaxation and which begins about 0.10 second earlier, at the onset of the second heart sound, and is simultane-

ous with the rapid descent of the carotid incisura (Fig. 4).

Tracings recorded from the epigastrium exhibited marked variability from subject to subject during this portion of the cycle.

Comment: Braunwald et al.[1,2] found that filling of the left ventricle apparently occurred 0.10±0.03 second after the second heart sound, and, therefore, at 0.06±0.03 second after the carotid incisural notch. Since the tracings regularly displayed an outward movement of the precordium at this time, it is highly probable that this motion is produced by ventricular filling. This upstroke occurred slightly earlier in the lower than in the superior portions. This would suggest that the lower parts of the ventricles fill before the upper parts. Prinzmetal's[8] rapid pictures of the dog's heart indicate that the inflow tract fills before the outflow tract, and these data offer indirect evidence that the same is true in man.

In some subjects the traces from the upper right parasternal region displayed inward motion, which was simultaneous with the outward motion in the left parasternal region of the same subject. This observation is interpreted as meaning that in such subjects the right parasternal traces tended to reflect emptying of the right auricle rather than filling of the right ventricle. It was hoped initially that study of different areas might allow one to distinguish between the filling of the two ventricles. However, this hope was not realized. Insofar as could be judged by the precordial records, they appeared to fill simultaneously in normal subjects.

Comment

The initial purposes of this study were to determine whether the precordial movements could be properly utilized as an index to the time of onset of ejection and filling of the ventricles and, if so, to learn which of the numerous possible precordial recording points would afford the most valid information. It would appear that the objectives of the study have been realized in part but not *in toto*.

The kinetocardiogram appears to furnish a valid guide, in most normal subjects, to the onset of right ventricular ejection. Thus the combination of a sharp downstroke at the K_{14} and K_{23} regions with an abrupt upstroke at the K_{25} and apical areas, when occurring simultaneously with each other and when occurring 0.03±0.02 second before the carotid upstroke, would appear to furnish clear evidence of right ventricular ejection.

The evidence in the precordial movements for the onset of left ventricular ejection is less definite. In most records, traces from the region of the P. M. I. display either the onset of an upstroke or a bend and increasing steepness of the preexisting upstroke. Likewise, some of the subjects displayed an upstroke in the left axillary and left epigastric regions, beginning about 0.105 second after the QRS onset. However, a simpler and perhaps more reliable method of determining the beginning of left ventricular ejection would appear to be to use the carotid upstroke, subtracting 0.02 second from its time of onset. This technique would appear to yield a figure within 0.01 second of the correct time of the start of left ventricular ejection.

The kinetocardiogram thus displays characteristic changes occurring at approximately the time of ejection, as determined by catheterization and by direct-puncture methods.[1-3] Actually, the movements of the precordium which we are attributing to the ejection are about 0.005 second later in the case of both ventricles. This minimal delay may be due to the slower heart rates of our subjects, who were not subjected to a discomforting procedure, or possibly to an actual or apparent lag in the precordial movements.

Evidence for the time of onset of ventricular filling appears to be best obtained from the lower left parasternal region, i. e., from the K_{25} and K_{26} traces. The upper portions of the precordium appear to move out slightly later than the lower areas.

In the studies of normal precordial motion, it is important to know the number of areas from which traces should be made. The present study would suggest that insofar as one is concerned with detection of movements related to the onset of ejection and of filling, adequate information can be obtained in most normal subjects by securing records from the K_{14}, K_{23}, K_{25}, or K_{26} points and from the exact spot of the P. M. I. If these records fail to show the characteristic features of right ventricular ejection 0.085 second after the onset of the QRS complex and of left ventricular ejection about 0.02 second before the carotid upstroke, it may be worth while to obtain records from the right and left epigastric areas and from the left axilla.

Even though most of the information desired concerning precordial movements in normal subjects can be obtained from the four areas mentioned above, there is as yet no certainty that traces from the same regions will yield maximal information in persons with abnormal hearts, and it would appear that for the present it is wise to secure records from numerous points in such subjects until more is known about the most desirable regions.

The foregoing discussion has dealt with the findings by both the funnel technique, which indicates the motion of a single point in relation to the movement of the surrounding parts of the chest and the crossbar method, which measures the absolute motion of a point of the precordium. The findings were very similar in most respects, but a few minor differences were noted. Among these were the following: 1. The motions of a given side of the chest were more constant with the crossbar procedure. Thus the differences between the K_{23} and K_{25} areas, which usually exhibited inward and outward motion, respectively, at about 0.085 second after the onset of the QRS when recorded with the funnel, were less apparent with the crossbar technique. 2. An inward movement of the right parasternal area at the onset of left ventricular ejection was rarely seen when the funnel method was used but was often visible with the crossbar technique. The latter traces frequently exhibited a sharp exaggeration of the previous inward motion. 3. The biphasic character of the apex thrust was less frequently seen with the crossbar than with the funnel tracings. 4. The outward motion commonly recorded in the right epigastric region at about 0.09 second after the QRS onset and ascribed to footward recoil of the right ventricle was not seen in any of the traces made with the crossbar technique. However, the outward movement occurring about 0.02 second later in the left epigastrium, and thought to represent left ventricular recoil, was observed with both methods. 5. The higher frequency heart sound vibrations were more commonly recorded with the crossbar than with the funnel method. Aside from these relatively minor differences, the findings by the two techniques were essentially identical.

One of the striking features of traces obtained from patients with coronary artery disease is the presence in many subjects of an abnormal systolic bulge (Fig. 7). Among the purposes of the present investigation was the elucidation of those precordial areas in which systolic bulges may normally occur. It would appear that during ejection the precordial trace may remain above the diastolic baseline in the case of records taken with the funnel technique from the right parasternal area (Figs. 1 and 2) and from the upper portions of the precordium, i. e., from the left third and fourth interspaces. On the other hand, we have not yet encountered a normal subject in whom the record secured from the left lower precordium (fifth and sixth interspaces) remained above the baseline throughout ejection (Figs. 3 and 4). Therefore, it would appear that a record displaying a prolonged systolic bulge above the baseline in the left fifth or sixth interspaces is in all probability abnormal. On the other hand, a bulge above the baseline in the right parasternal region or in the left third or fourth interspaces should not per se be interpreted as an abnormal phenomenon.

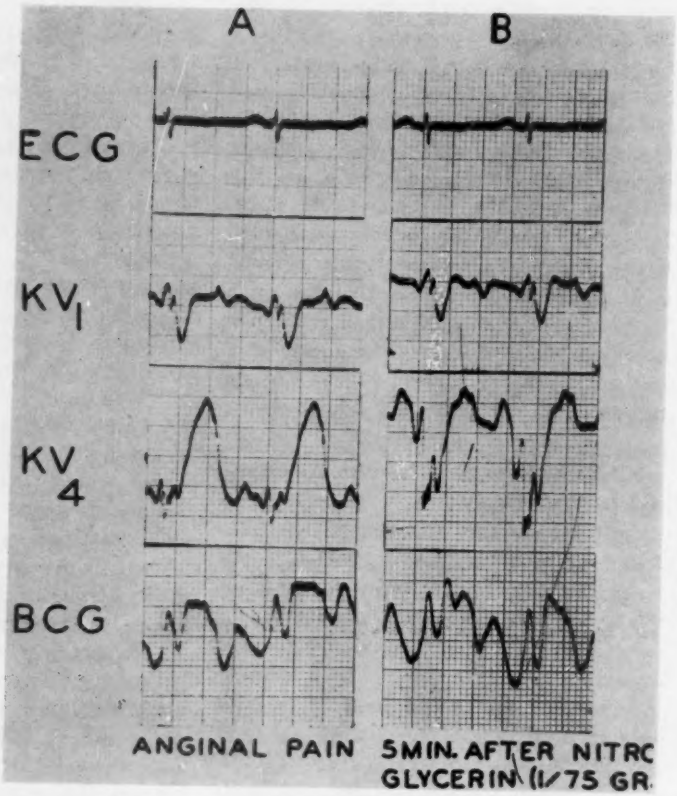

Fig. 7.—Camera speed, 25 mm. per second. Crossbar technique. The subject experienced a spontaneous attack of angina while the traces were being made. The K_3 (right parasternal) record remained normal, but striking abnormalities were noted in the K_4 (apex) trace. During the pain the normal early systolic retraction of the apex was diminished; the movement corresponding to the apex thrust was very small, and the inward movement of ejection was represented by a small notch only. This was immediately followed by a pronounced systolic bulge beginning 0.16 second after excitation, and the trace remained above the diastolic baseline throughout the remainder of systole. Following the administration of glyceryl trinitrate (nitroglycerin) and the relief of pain, the apex thrust and the inward movement of ejection increased but were still small. The early systolic retraction became normal, and the outward movement in midsystole was still striking but did not extend significantly above the diastolic baseline. Therefore, the pronounced systolic bulge disappeared. The K_4 record and the BCG were still abnormal, but less so than during the attack of pain.

The movements related to ejection and filling are by no means the only features of the precordial traces. During auricular contraction, during the preejection phase of systole, and during relaxation there are consistent motions. The genesis of these movements will be the subject of future studies. Such studies will be clarified by an understanding of those movements which are related to ejection and to filling.

Summary

Low-frequency precordial motions (kinetocardiograms) of 36 normal male subjects were analyzed in relation to the onset of ventricular ejection and filling. The more pertinent findings were as follows:

1. At 0.087±0.018 second after the start of ventricular excitation the right parasternal and the upper left parasternal regions move sharply inward. This is attributed to volume change as the right ventricle ejects. At the same time outward motion is observed in the apical and lower parasternal regions. This is ascribed to recoil of the heart as the right ventricle ejects.

2. At 0.105±0.015 second after the onset of the QRS and 0.02±0.01 second before the start of the carotid upstroke the left epigastric area moves outward and the sec-

ond portion of the biphasic apex thrust begins. These outward movements are interpreted as representing footward, forward, and leftward recoil as the left ventricle ejects.

3. At 0.48±0.05 second after excitation and 0.06±0.04 second after the carotid incisural notch, the left parasternal and apical regions move outward. This is believed to represent simultaneous filling of the two ventricles.

4. In the right parasternal and the upper left parasternal regions, the initial inward movement of ejection is soon followed by outward motion, which may extend above the diastolic baseline. In the lower left parasternal and apical regions, this inward movement is either absent or minimal and does not extend above the diastolic baseline. In these latter regions a large prolonged outward motion during ejection is to be regarded as abnormal.

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The Clinical and Surgical Aspects of Chronic Pulmonary Artery Thrombosis

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An experience with two cases of subacute cor pulmonale due to thrombosis of the trunk and major branches of the pulmonary artery has brought into focus the possibility of a surgical approach to the treatment of this disease. The clinical and anatomic features of the first case suggested the possibility of making an accurate clinical diagnosis and of managing the problem surgically. The second case report represents the first planned attempt surgically to relieve the obstructive phase of chronic cor pulmonale due to pulmonary artery thrombosis.

Report of Cases

CASE 1.—A 62-year-old white woman was admitted for the second time to Montefiore Hospital on Jan. 11, 1956, because of severe and increasing dyspnea of approximately 10 hours' duration. She was initially admitted on Dec. 16, 1955, because of an enlarged obstructing thyroid gland which compressed the right recurrent laryngeal nerve. On Dec. 29, 1955, a subtotal thyroidectomy was performed. The postoperative course was uneventful. Histologic examination of the thyroid revealed an adenomatous goiter. The patient was discharged on Jan. 8, 1956. Of interest is the fact that during the first hospitalization preoperative studies revealed a normal venous pressure of 60 ml. of water, rising to 65 ml. on right-upper-quadrant pressure, and a dehydrocholic acid (Decholin) circulation time of 21 seconds. Posteroanterior and lateral x-rays of the chest disclosed slight accentuation of the interstitial structures, with pleural changes at both bases. The heart was considered to be borderline in size, with calcification of the aortic arch. An electrocardiogram was described as showing a normal sinus rhythm, with slight depression of the ST segments in Leads I and aV_L and aV_8. This was interpreted as nonspecific ST-segment changes. The hematocrit was 41%.

The patient was well until the morning of the second admission, when she awoke with severe shortness of breath, dizziness, and a cold sweat. She complained of a vise-like pain in the epigastrium and substernal region, which radiated to the scapula. This pain was associated with persistent numbness of the finger tips. There was no history of a similar episode. The patient was in acute distress, with dyspnea, orthopnea, restlessness, and confusion. Temperature was 101 F; pulse rate, 130, and respiration, 35 per minute. The blood pressure was 132/70 on the right and 128/70 on the left. The neck veins were not distended; the trachea was in the midline; the thyroidectomy scar was well healed. The lungs were clear to percussion and auscultation, except for an occasional wheeze posteriorly over both lower lung fields. The heart sounds were distinct; no murmurs were heard. The second pulmonic heart sound was equal to the second aortic sound. The liver and spleen were not palpable. Slight tenderness was noted in the right upper quadrant. Peripheral edema and ascites were not present. Laboratory studies revealed a leukocyte count of 13,900, with 78% polymorphonuclear leukocytes and 23% lymphocytes, 2% eosinophiles, and 2% monocytes. The hematocrit was 38%. The urine concentrated to 1.022 and revealed 1+ albuminuria. An anteroposterior chest film taken with a portable machine was reported as showing an enlarged cardiac silhouette, with prominence of the pulmonary artery and bilateral pulmonary vascular engorgement. The electrocardiogram revealed left axis deviation, with a negative T wave in Lead I.

Oxygen and intravenous fluid were administered without improvement. Dyspnea, mental confusion, feelings of faintness, and substernal oppression continued. In the next 48 hours she had two syncopal attacks. The course was further complicated by the development of diarrhea, with pain and marked tenderness in the left lower quadrant of the abdomen; a questionable mass appeared in the right upper quadrant. An acute peritonitis and possible empyema of the gallbladder were considered. These findings, however, subsided spon-

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taneously. Serial electrocardiograms were taken, but no definitive diagnosis could be established. The possibility of an anterior-wall myocardial infarct was entertained, but the findings were not diagnostic. The venous pressure was 150 ml. of water, with a rise to 200 ml. on right-upper-quadrant pressure. Circulation time determined twice, with use of sodium succinate, was 37 and 62 seconds, respectively. Fever, dyspnea, and tachycardia persisted. On Jan. 22, 1956, twenty-four days after thyroidectomy and eleven days after readmission to the hospital, the patient developed circulatory collapse. The blood pressure dropped to 60/30. The respirations increased markedly, but in spite of this the lungs remained clear to percussion and auscultation. Levarterenol (Levophed) was administered in an attempt to elevate the blood pressure, but the patient died.

At autopsy the right lung weighed 750 gm. The left lung weighed 700 gm. There were no areas of consolidation. On section, the lungs were moderately edematous. The trachea and bronchial tree were unremarkable. In the left pulmonary artery there was a large adherent thrombus, the ramifications of which filled the smaller branches. This thrombus measured 4.0×4.5 cm. and showed early organization. The main and right pulmonary arteries contained no thrombi. The heart weighed 440 gm. The right ventricular myocardium measured 0.4 cm., and the left ventricular wall, 1.6 cm. in thickness. There was hypertrophy and dilatation of the right side of the heart. There were no thrombi in the auricular appendages. The heart was otherwise unremarkable. Small thrombi were found within the pelvic veins. There were no other significant pathological findings.

Comment.—This patient's course is an example of acute cor pulmonale secondary to thrombotic obstruction of a major pulmonary artery. The organizing thrombus was probably superimposed on an embolus which arose in the peripheral veins. There was little in the clinical findings to indicate peripheral venous thrombosis, although the acute onset of intractable dyspnea, substernal pain, and syncope, with subsequent development of increasing right ventricular failure and eventual circulatory collapse, are strongly suggestive of increasing pulmonary hypertension. Although the electrocardiogram did not reveal right ventricular strain, the x-ray indicated dilatation of the pulmonary artery. Sufficient time elapsed between the acute onset and death to have permitted surgical intervention, as described below.

Case 2.—A 53-year-old white woman was admitted to Montefiore Hospital on Jan. 26, 1957, because of increasingly severe dyspnea and cyanosis of 24 hours' duration. The past history, related by the patient's personal physician, is significant. Thirty years ago, following her first pregnancy, the patient had an episode of thrombophlebitis. She was apparently well thereafter until 10 years ago, when she began to develop recurrent episodes of dyspnea which were interpreted as being due to congestive heart failure. Digitalis, low-salt regimen, and diuretics were prescribed with no apparent benefit. There was no previous history suggestive of rheumatic fever. No murmurs were heard at any time. The blood pressure was always in the normotensive range. The electrocardiograms did not, at any time, reveal any evidence of coronary insufficiency or myocardial infarction. Six years ago the patient's physician found the heart to be enlarged on fluoroscopic examination. One year prior to admission the patient developed thrombophlebitis involving both lower extremities. She was hospitalized shortly thereafter because of an episode of chest pain and hemoptysis. A chest x-ray at that time revealed an infiltrate in the left upper lobe, which cleared after an interval of months. Since then she has had increasingly frequent episodes of dyspnea which were refractory to digitalis and mercurials. Cyanosis of the lips and nail beds was first noted six weeks prior to admission.

On admission physical examination revealed an acutely ill severely dyspneic woman, with marked cyanosis. The pulse and blood pressure were unobtainable; the neck veins were engorged; a patch of fine crackling rales were heard at the right base posteriorly. The heart sounds were distinct and of fair quality. The second pulmonic sound was greater than the second aortic sound. A proto-diastolic gallop was heard at the apex. There were no cardiac murmurs. The liver was palpable 3 fingerbreadths below the right costal margin. The spleen was not felt. There was no ascites. There was slight pitting edema of both lower extremities. A positive hepatojugular reflex was observed. Laboratory examination revealed a hematocrit of 55%; the white blood cell count was 8850. Urinalysis revealed albuminuria (3+), glycosuria (1+), and 2 to 4 leukocytes per high-power field. Venous pressure was 300 ml., with a dehydrocholic acid circulation time of 70 seconds. The electrocardiogram revealed regular sinus rhythm, with peaked P waves in Leads I and II and marked right ventricular preponderance. An anteroposterior chest roentgenogram taken with a portable machine disclosed a markedly enlarged and

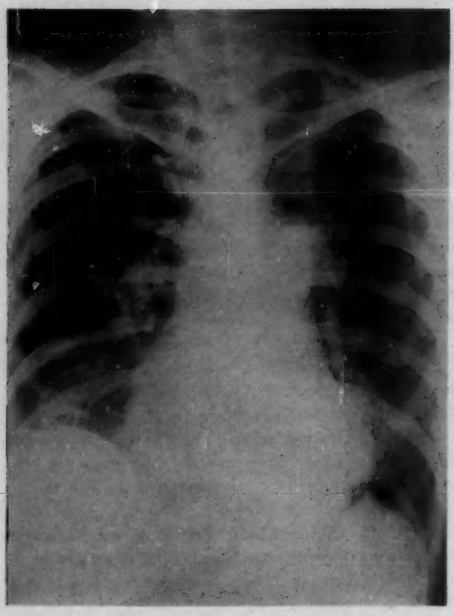


Fig. 1A.—Film of the chest taken 17 months prior to present admission. The pulmonary artery is prominent and enlarged; the lungs are clear.

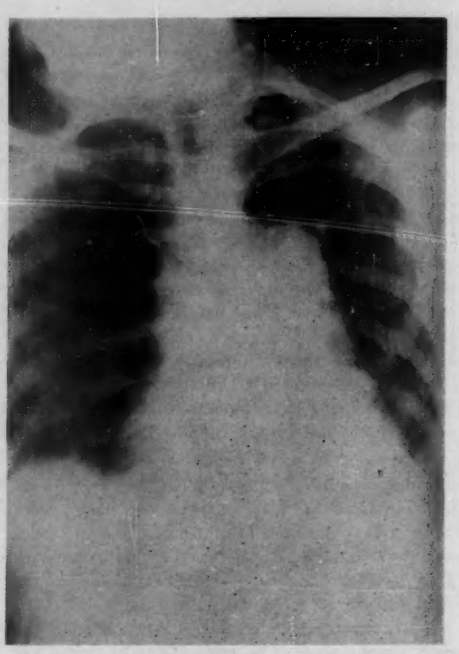


Fig 1B.—Anteroposterior 4 ft. film taken with a portable machine on the day of operation. Although the patient is rotated and there is motion, the findings are striking as far as the degree of enlargement of the pulmonary artery is concerned. The lungs are clear.

opacified pulmonary artery segment, with increase in the transverse diameter of the heart. The lung fields were clear, but a pleural reaction was noted at both bases. A diagnosis of thrombosis of the pulmonary artery was made, and surgery was considered imperative (Fig. 1).

The patient was practically in extremis when she reached the operating room and had to be kept in the sitting-up position. Intratracheal intubation and a light plane of anesthesia were quickly accomplished. Correction of the obstruction to right ventricular outflow by direct removal of the thrombus from the pulmonary artery was contemplated. Because of the patient's critical condition, it was not possible to take the time to obtain a level of hypothermia which would permit prolonged periods of venous inflow occlusion, as in the operation of open pulmonic valvulotomy. Instead, it was hoped that thrombectomy might be effected by employing one or more short (less than three minutes) periods of vena cava occlusion. Both pleural cavities were entered in the third interspaces anteriorly by a transverse incision, transecting the sternum (E. S. H.). The pericardium was opened, and tapes were passed around the superior and inferior venae cavae. The right auricle and ventricle were huge. The main trunk of the pulmonary artery was dilated and free of clot. Just below the bifurcation the main pulmonary artery was occupied by a solid mass, which extended into the right and left main pulmonary arteries as far as the roots of both lungs (Fig. 2). Through an incision in the trunk of the pulmonary artery, large amounts of adherent organized clot were expressed from the region of the bifurcation and the left pulmonary artery. The inflow occlusion was released after two and one-half minutes, with the intention of clearing the right pulmonary artery after a period of restoration of the circulation. However, cardiac arrest had developed which was refractory to all efforts at resuscitation. The details of this operation are described in a separate communication.[4]

At autopsy the right lung weighed 400 gm. and the left lung, 375 gm. There was a cavity with a fibrous wall representing an old infarct at the left apex. An organizing infarct was present in the left lower lobe. The main trunk of the pulmonary artery was greatly dilated but free of thrombus. The right main pulmonary artery contained a dense friable yellow thrombus. This was adherent to the anterior, superior, and inferior aspects of the main branches. Posteriorly, there was a narrow semilunar slit which was patent. The thrombus extended across the bifurcation but did not enter the main trunk. It extended out to the lobar

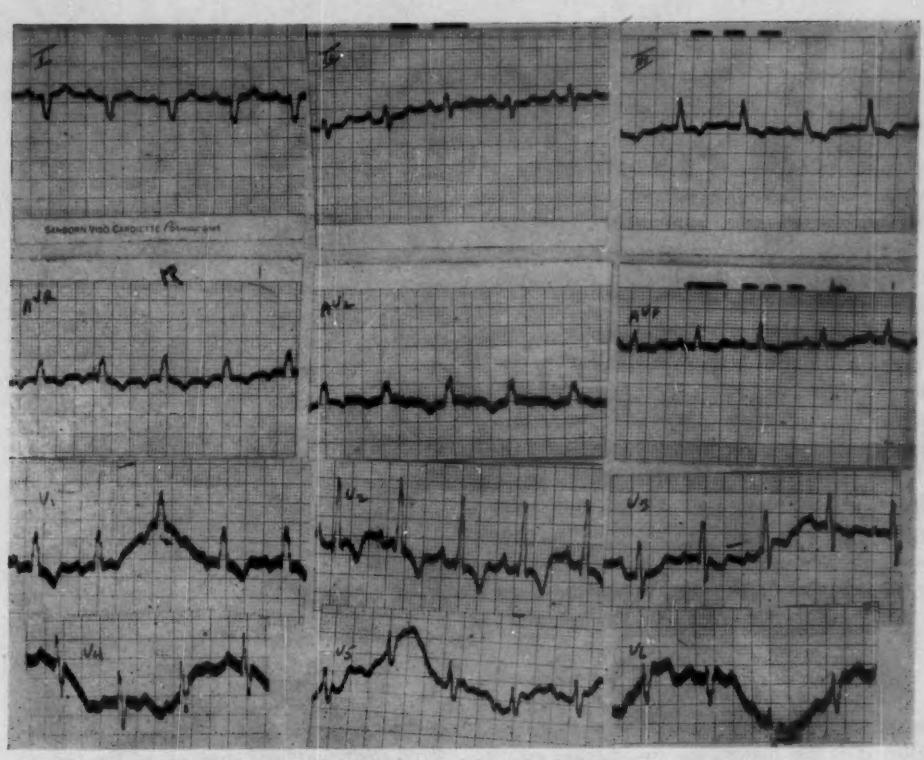
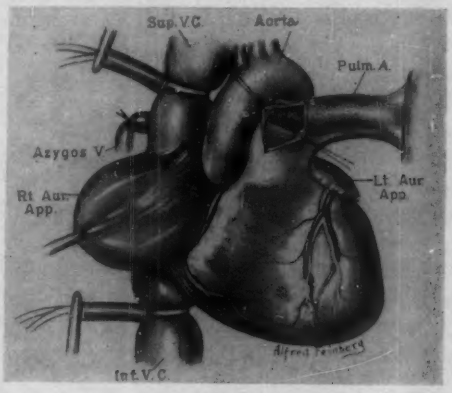


Fig. 1C.—Final electrocardiogram shows right axis deviation.

branches. A few of the segmental branches were also involved. On the left the thrombus was fragmented, large portions of it having been removed surgically. On section of the thrombus in the right pulmonary artery, the posterior surface was covered by a red layer which appeared to be of more recent origin than the remainder. Within the pulmonary parenchyma there were red gelatinous thrombi occluding one arterial segmental branch to the right middle lobe and one to the right upper lobe. There was a somewhat firmer adherent brown-red thrombus occluding an arterial branch to the left lower lobe in the region of the infarct. These were propagating portions of the major thrombus which had broken off. The heart weighed 400 gm. The right ventricular myocardium was 0.8 cm. in thickness, and the left ventricular myocardium, 1.2 cm. in thickness. The heart was dilated and flabby. There was marked dilatation and hypertrophy of the right auricle and ventricle. The pulmonary conus was widened. The apex of the right ventricle extended below the apex of the left ventricle. There was a 1×2 cm. adherent gelatinous thrombus in the right auricular appendage. Section through the base revealed a gray line, suggesting organization. The heart was otherwise unremarkable. The superior and inferior vena cavae and the iliac, femoral, and pelvic veins contained no thrombi.

Histologic examination revealed that the thrombus in the main branches was composed of

Fig. 2.—Diagram of venous inflow occlusion and pulmonary arteriotomy; ligation of azygos vein may be avoided by intrapericardial occlusion of superior vena cava.



layered fibrin, hyalinized in the deeper layers and interspersed with fresh red blood cells close to the lumen. There were focal collections of polymorphonuclear leukocytes scattered throughout the myocardium. These were felt to be a response to prolonged anoxia. In the left popliteal vein there was an eccentric subintimal fibrous plaque which was interpreted as the residuum of an organized thrombus.

Comment.—This case exemplifies the syndrome of chronic thrombosis of the pulmonary artery. There is a past history of venous thrombosis of the legs, recurrent episodes of dyspnea unresponsive to the usual cardiac regimens, increasing evidence of right ventricular heart failure, and, finally, sudden circulatory collapse. The clinical diagnosis was further supported by the roentgen finding of a dilated pulmonary artery segment which was noted in the x-ray taken on admission and which was present in the films made three years previously.

Comment

The incidence of major pulmonary artery thrombosis is almost impossible to establish. It is the history of any disease entity that the apparent incidence increases as more accurate laboratory aids to diagnosis appear and as a mode of therapy is offered for a condition previously of academic interest only.

Bryson attributes the first reported case to Heile, in 1837.[22] In 1934, Kampmeier reviewed the literature and added one case, bringing the total at that time to 34.[69] The reports of Pou and Charr, in 1938,[100] and of Savacool and Charr, in 1941,[106] brought the total experience to 100 cases. Other series were reported as follows: Ball et al., 23 cases[5]; Belt, 4 cases[8]; Carroll, 5 cases[24]; Crawford and Mohler, 30 cases[38]; Davison et al., 3 cases[40]; Desclin, 8 cases[41,42]; Gunter, 2 cases[54]; Hanelin and Eyler, 5 cases[56]; Hollister and Cull, 2 cases[62]; Keating et al., 7 cases[70]; Kyser, 14 cases[73]; Magidson, 9 cases[83]; Owen et al., 12 cases,[97] and Ring and Bakke, 21 cases.[102] There are individual case reports by Schneider and Van Ordstrand,[107] Covey,[37] Pitts and Sparks,[99] Levy et al.,[76] Conklin and Litwin,[36] Boucher et al.,[17] Means and Mallory,[87] Canada et al.,[23] Meilman,[88] Montgomery,[93] and Bostock.[15]

The incidence has been variously estimated. Clawson reported five cases of thrombosis or embolism in 30,265 autopsies.[34] Fowler reported 6 cases in 939 consecutive autopsies[49]; Brenner reported 4 cases in 100 autopsies,[19,20] and Lenegre and Gerboux collected 14 cases in 706 autopsies.[74] Middleton reports 53 cases encountered over a 16-year period at the Wisconsin General Hospital.[90] There are extensive tabulations of the literature by Fowler,[49] Brenner,[19,20] and Möller.[91]

The total published experience is estimated at approximately 300 cases. The vast majority of these are from postmortem material. In recent years, the diagnosis is being made with increasing frequency and confirmed by angiocardiography and right-sided cardiac catheterization.

Pulmonary artery thrombosis is frequently secondary to congenital and acquired cardiovascular disease. In the former instance it is observed in pulmonic valvular stenosis, tetralogy of Fallot, and septal defects and at the site of multiple or solitary pulmonary artery aneurysms. In acquired heart disease it is reported as secondary to mitral stenosis, myocardial infarction with mural thrombosis, syphilitic arteritis, thromboangiitis obliterans, and sickle-cell disease. In this group of patients the pulmonary thrombosis appears as a consequence of polycythemia, stasis, or obstruction. The clinical features of the dominant disease often mask and obscure the changes in the pulmonary artery. There is a second group of patients, whose thrombosis is initiated within an artery which courses through an area of contiguous disease. This is usually observed in association with pulmonary tuberculosis, mediastinal metastatic carcinoma, and bronchogenic carcinoma.

Of the 299 reviewed cases,[1-8,10-12,14-16,18-38,40-54,56-62,65-93,95-113] mitral stenosis was present in 34; congenital heart disease

(tetralogy of Fallot, pulmonic stenosis, septal defects), in 8; pulmonary tuberculosis, in 33; chronic bronchitis, emphysema, and pulmonary fibrosis (including one case of Boeck's sarcoid), in 18. Pulmonary and mediastinal tumors were present in seven cases; acute contiguous disease (pneumonia, lung abscess), in seven, and syphilitic arteritis, in two. Two cases of leukemia and one of chlorosis were found. In 10 cases the thrombosis appeared to be a preterminal or agonal event in patients with acute sepsis or severe debilitation and dehydration.

There is another group, of 177 cases, in which the subacute and chronic thrombosis of the pulmonary arteries is the primary cause for the enlargement of the right heart and subsequent cardiac failure. Pulmonary-artery thrombosis of this type may occur as a result of the organization of pulmonary emboli, of an autochthonus thrombus on an atherosclerotic plaque, or following severe chest trauma. It is toward this concept of primary pulmonary artery thrombosis that this paper is oriented.

It is frequently impossible, even at postmortem examination, to determine whether or not pulmonary thrombosis has its source in a peripheral venous thrombus. Cohen [35] and Glynn [52] regard spontaneous thrombosis as commoner than that arising from peripheral emboli. Their criteria, however, are concerned with lamination, degree of adherence, the contour of the thrombus, and the presence or absence of recanalization. Brenner [20] points out that these characteristics are the same in an autochthonus thrombus as in the propagated portion of a thrombus arising from an embolus. The superimposition of a thrombus upon an atherosclerotic plaque is not an assurance that the thrombus is autochthonus. In long-standing obstruction of the pulmonary arteries the proximal portions may become thickened and develop atheromata which are then engulfed by the propagating thrombus. The discovery of venous thrombi at postmortem examination is not a priori evidence of a cause-and-effect relationship. Obstruction to the lesser circulation gives rise to venous congestion and peripheral edema, predisposing to venous thrombosis. The presence in the smaller vessels of fibrous intimal thickening and atheromata is not diagnostic of primary pulmonary arteriosclerosis. These findings have been duplicated experimentally by intravenous injection of macerated clot.[94,114] They occur in patients with known repeated embolization.[97] From a practical point of view, directed toward the living patient rather than the autopsy subject, it is not possible to differentiate pulmonary embolism with subsequent thrombosis from an autochthonus thrombus without a definite history of either phlebitis or an embolic episode. The distinction is of importance because it influences the total surgical approach to the management of established pulmonary artery thrombosis and cor pulmonale. There are, however, well-documented cases of pulmonary artery thrombosis which occurred following clinically proved iliofemoral thrombophlebitis in which no thrombi could be found in the legs or pelvis. The contrary situation is also frequent. Here the pulmonary artery obstruction is the sole presenting symptom of previously unrecognized venous thrombosis. Unless there is good reason to implicate local pulmonary artery disease or trauma, these cases are best regarded as being embolic in origin.

It is doubtful that these thrombotic processes result from organization of an embolus involving the trunk and bifurcation directly, since such cases are usually rapidly fatal. Davis et al. have shown that experimental occlusion of the pulmonary artery in monkeys for 50 hours results in thrombus formation at the site of occlusion, with propagation extending into the branches.[39] There are many reports of thrombi involving only one stem of the pulmonary trunk, the majority occurring on the right side. The preponderance of right-sided involvement is believed to be due to the longer course of this artery and the fact that it may be compressed by the arch of the aorta

and the right main-stem bronchus. The base of the pulmonary artery trunk and its supraventricular component have been found to be involved only once. Kornbluth and O'Hara report a case with a thrombus extending to the semilunar cusps.[71] Usually the base of the pulmonary artery is normal, the only change being marked dilatation occurring proximal to the thrombus. The thrombus may extend to involve the lobar and even the lobular divisions of the pulmonary artery. However, many cases of pulmonary artery thrombosis are limited to the trunk and the two major branches. The localization of thrombi with regard to this anatomic disposition is tabulated in a separate publication.[64] Once the thrombus has been established, the course of the disease depends upon the degree of occlusion to the outflow tract of the right ventricle and the presence or absence of episodes of pulmonary infarction. In most cases there is no evidence of recent pulmonary infarction. The changes that are observed in the heart are solely those resulting from obstruction and are characterized by dilatation and subsequent hypertrophy of the right ventricle and auricle.

One of the striking features of this type of cor pulmonale is the very variable period for which the pulmonary outflow tract obstruction may be tolerated. There is an antecedent history compatible with "idiopathic" right-sided failure with increasing dyspnea, leading to rapidly increasing failure and sudden death. In the table is tabulated some of the published experience regarding the time interval between the onset of right-sided failure and sudden death. This phenomenon is related to the degree of obstruction within the cross sectional diameter of the pulmonary artery. In the experimental animal, Gibbon, Hopkinson, and Churchill have shown that a minimum of 60% obstruction of the pulmonary artery outflow is required to produce a fall in systemic blood pressure; 90% occlusion is fatal.[51] Haggart and Walker have demonstrated in cats that until 52% to 66% of the pulmonary circulation is obstructed there are no significant changes in cardiovascular dynamics.[55] The end-point at which failure appears is definite and sharp. The clinical situation is analogous.

Cases of Chronic Pulmonary-Artery Thrombosis with Potential Surgical Salvage *

Author, Year	Infarcts †	Peripheral Source †	Duration of Symptoms, Mo.
Ball et al.,[8] 1956	0	+	0.5
	0	Hist.	28
	Mass.	0	--
Belt,[9] 1939	0	+	4
Billings,[10] 1921	+	0	0.3
	+	0	0.7
Carroll,[14] 1950	Mult.	+	24
	Mass Mult.	+	14
	Mult.	+	2
	Mult.	0	2
Covey,[17] 1943	Mult.	+	12
Davison et al.,[40] 1956	0	+	24
Desclin,[41] 1930	Hist.	+	15
	0	+	--
	0	+	3
	0	0	1.5
Fowler,[43] 1934	0	0	6
Goedel,[53] 1930	0	0	0
Hollister & Cull,[59] 1956	Mult.	+	1
	0	+	18
Keating,[79] 1953	0	0	18
	0	0	18
	0	0	6
	Hist.	Hist.	8
Ljungdahl,[78] 1928	0	0	36
	0	0	18
Magidson & Jacobson,[80] 1955	0	+	12
	Mult.	0	74
	0	+	--
	0	0	--
	+	0	6
	0	0	1
Mönckeburg,[91] 1907	0	0	5
Montgomery,[93] 1935	+	0	18
Owen et al.,[97] 1953	0	+	38
	0	+	1.5
	+	0	6
Ring & Bakke,[103] 1955	+	0	12
	0	+	0.1
Schneider & Van Ordstrand,[107] 1940	Mass.	+	48
Sebein et al., 1957	0	+	0.3
	Mult.	+	120

* These data have been collected from the reports of the authors indicated in the first column. No cases are tabulated except those in which the information is definite and conclusive. Each horizontal line represents a single case.

† Hist. indicates by history only; Mass., massive; mult., multiple.

These patients maintain an adequate pulmonary aeration with almost total arterial occlusion, especially if the thrombosis develops slowly. The bronchial-pulmonary artery anastomoses and collateral vessels maintain the blood flow to the lungs. Although the bronchial and pulmonary arterial systems are normally independent, they have a common capillary anastomosis which also communicates with the pulmonary veins. When the pulmonary artery is occluded, there is a fall in pressure in the common capillary bed; this lowers the peripheral re-

sistance to the systemic pressure of the bronchial arteries. In the experimental animal with a ligated pulmonary artery the capacity of the lung to maintain oxygen and carbon dioxide exchange actually increases over a period of months.[9,13] When the pulmonary artery is completely blocked the systemic circulation is brought to an end regardless of the collateral circulation. The entire syndrome of right-sided failure is related directly and solely to the occlusion of the right ventricular outflow tract. The sudden death is directly correlated with complete obstruction of the pulmonary artery by propagation of the thrombus or additional fresh embolization to the artery. Death may also occur as the result of occlusion of an associated septal defect which had served as an outlet for the obstructed right side of the heart.[94]

The symptoms and signs of chronic thrombosis of the major pulmonary arteries vary, but a characteristic group of clinical findings are present which should suggest the diagnosis during life. Our second case appears to be almost classical in terms of past history, presenting complaints and clinical findings in addition to the corroborating roentgenographic and electrocardiographic data. The predominant presenting symptom in almost all case reports is severe and intractable dyspnea. A history of previous attacks of paroxysmal nocturnal dyspnea may be elicited, but this is unusual. Episodes of repeated pulmonary infarctions are not invariably noted. When present, they are often associated with a definite peripheral source for the pulmonary embolus. Pleuritic pain and hemoptysis, when present, are associated with pulmonary infarction, but in some cases the hemoptysis has occurred in the absence of infarction of the lung and may be the result of ruptured anastomotic channels represented by bronchopulmonary anastomotic collaterals. Frequently a history of substernal pain, occasionally radiating to the back and to both shoulders, can be elicited. This is probably associated with acute pulmonary hypertension and is presumably due to diminished coronary blood flow. Often, mental confusion and recurrent syncopal attacks are cited and result from decreased cerebral blood flow.

The typical physical findings are those of right ventricular heart failure, namely, hepatic congestion, increased peripheral venous pressure, and peripheral edema. Although an accentuated second pulmonic heart sound is frequently noted, a normal second pulmonic heart sound is heard occasionally and probably reflects the extremely low pressure in the pulmonary artery, which results from the extension of the thrombotic occlusion. Systolic as well as diastolic murmurs over the pulmonary artery have been described, but in a number of case reports no murmurs were heard. A decreased cardiac output is responsible for the hypotension, restlessness, and signs of vascular collapse. Determination of venous pressure, circulation time, and vital capacity do not directly aid in the diagnosis but help in the early detection of congestive heart failure. The hematocrit is often unchanged. The electrocardiograms frequently, but not invariably, reveal evidence of right ventricular enlargement. Other electrocardiographic interpretations reported in the literature include right axis deviation and the patterns usually associated with posterior myocardial infarction and the low-potassium state. The roentgen criteria in this clinical entity have been established.[56,70,111,115] The most significant findings include dilatation of the pulmonary artery proximal to the occlusion, with enlargement of the vessel at the level of the thrombus and a decrease in the caliber of the branches distal to the thrombus. An increased radiolucency in the corresponding lung, producing the effect of clear lungs, is the result of pulmonary ischemia. There is also evidence of right ventricular enlargement. Fluoroscopically, absent pulsations in the enlarged main pulmonary arteries have been described and are of particular significance in patients who have been examined previously. The combina-

tion, then, of clear lungs and enlarged pulmonary arteries is of real diagnostic value.

Cardiac catheterization confirms the presence of right ventricular hypertension with low cardiac output and is of further aid in excluding such lesions as septal defects and pulmonic stenosis. The latter disease may be impossible to exclude with certainty in view of the difficulty encountered in passing a catheter into an extensively thrombosed pulmonary artery. Pressure in the pulmonary artery has been reported as 96/36 and in the right ventricle, as 80/20.[24] Angiocardiography has been described as a useful means of demonstrating obstruction in the major pulmonary arteries and would appear to be most helpful in confirming the diagnosis during life. Noteworthy in this regard is the experience of Dimond and Jones, who report regarding the angiographic confusion which may arise in this differential diagnosis.[44] In the acute stage, however, the patient is too ill for this procedure to be executed properly and one must rely on the available clinical data.

The diagnosis of pulmonary artery thrombosis should be seriously considered on the evidence of marked right-sided heart failure with dry lungs, indicating little or no evidence of left-sided failure. The diagnosis becomes even more probable with a past history of peripheral venous thrombosis, a normal second pulmonic heart sound, and a systolic murmur over the pulmonary artery. The diagnosis may be further supported if the electrocardiogram reveals right ventricular enlargement and the chest x-ray indicates enlargement of the right ventricle and dilatation of the pulmonary arteries with otherwise clear lungs or an infiltrate suggesting pulmonary infarction. The combined experience indicates that there is a latent interval which precedes the accelerated phase of complete outflow-tract obstruction. During this latent interval the symptoms and signs of an unusual type of cor pulmonale should suggest the possibility of pulmonary artery thrombosis. This interval is usually sufficiently long to permit accurate radiologic diagnosis and to allow time for a planned surgical approach. The hope for patient salvage lies in the diagnostic recognition and surgical ultilization of this interval.

The diagnosis of pulmonary artery thrombosis should also be entertained in a patient with progressively increasing right ventricular heart failure of unusual etiology who responds poorly to digitalization, sodium restriction, oxygen, and the usual diuretic agents and in whom dyspnea, cyanosis, syncope, and chest pain are noted.

Many conditions, however, must be considered in the differential diagnosis of chronic pulmonary artery thrombosis. Among these the most important are mitral stenosis, pulmonary stenosis, and interatrial septal defects. Idiopathic pulmonary hypertension, acute pulmonary infarction, constrictive pericarditis, lymphangiitic carcinomatosis, traumatic aneurysm, and chronic pulmonary fibrosis must also be considered and may be excluded by clinical history and the evidence provided by routine roentgen examination, cardiac catheterization, and angiocardiography.

Mitral stenosis frequently can be distinguished by the characteristic snapping first sound or localized presystolic apical murmur, although this may not be heard in patients with severe pulmonary hypertension, and, rarely, the presystolic component has been described in patients with primary pulmonary hypertension. Fluoroscopic and radiologic studies, particularly in the right antero-oblique position, usually show left atrial enlargement. Pulmonary stenosis with its typical loud systolic murmur and diminished or absent pulmonic second sound must be excluded. Cardiac catheterization and angiocardiography in patients with this condition frequently will reveal a poststenotic dilatation of the pulmonary artery associated with high right ventricular pressure and normal or low pulmonary arterial pressure. Interatrial septal defects reveal evidence of left-to-right shunt on cardiac catheterization, and, conceivably, the catheter

tip may be passed directly through the septal defect into the left atrium.

The syncopal episodes noted by patients with chronic thrombosis of the pulmonary artery must be distinguished from supraventricular or ventricular arrythmias, carotid sinus and vasovagal syncope, acute left ventricular failure or coronary insufficiency secondary to calcific aortic stenosis, acute myocardial infarction, venoarterial shunts, ball-valve thrombi of the mitral or tricuspid valves, and myxomas of the left auricle.

The possibility of a surgical approach to what is otherwise a uniformly fatal disease should depend upon careful selection of cases. Only primary pulmonary artery thrombosis should be considered, regardless of whether this is secondary to recurrent embolism, pulmonary arteritis, or trauma. If the suspicion of the clinician is aroused, the use of angiocardiography should be employed to confirm the diagnosis. Obviously, a favorable result would be more likely in cases operated on in the larval subacute or chronic phase of disease. Operation undertaken as an emergency procedure for total obstruction to the right ventricular outlet is done under the worst possible conditions. Even here it should be undertaken as the sole hope. In such instances it resembles in difficulty and prognosis the Trendelenburg pulmonary arteriotomy for acute embolic occlusion.

The location and extent of the intrapulmonary arterial propagation of the thrombus limits the possibility of definitive surgical therapy. From a review of the literature this would appear to be feasible in at least 10% of the reported cases. In these instances it should be borne in mind that the medical therapy of adequate phlebotomy and effective anticoagulation has rarely been successful. The past surgical experience with pulmonary artery thrombosis is limited. Carroll reports that Blalock explored a proved case of left-sided pulmonary artery thrombosis and divided the occluded artery.[24] Björk and Norhagen report a wedge resection of a portion of the left pulmonary artery in the course of a lobectomy for tuberculosis.[11] Boucher, Protar, and Bertein report a pneumonectomy for aneurysm and thrombosis of one pulmonary artery.[17] The procedure as here conceived has not been previously reported.

The most direct approach to the pulmonary artery is by a bilateral transsternal thoracotomy. The need for hypothermia with inflow occlusion or cardiac bypass with an oxygenator will depend upon the local situation as well as the stage of the disease in which the patient is seen. The details of surgical management are the subject of a separate publication.[64] The simplest procedure entails a thrombectomy, an operative procedure similar to that described by Leriche for thrombosis at the aortoiliac bifurcation. The pulmonary branches at the hila are isolated to prevent propagation of thrombotic material during the manipulation. The arterial reaming should be adequate to permit satisfactory egress of blood from the right ventricle. Prolonged adjuvant anticoagulation therapy is utilized to prevent thrombosis at the denuded site. Where the thrombus cannot be removed, arterial grafting may be the procedure of choice. Replacement of the main pulmonary artery and its bifurcation by aortic homografts has been accomplished in the experimental animal.[62]

If no other etiology for the thrombus can be established with certainty, it should be assumed to be embolic and the second phase of the operation should be directed at the peripheral venous system as part of the same operative procedure. If there is a history of repeated embolization, inferior vena cava ligation below the level of the renal veins is recommended. If there have been no phlebitic episodes, bilateral superficial femoral vein ligations and/or anticoagulation may be indicated.

Summary

The salient clinical, pathogenic, and diagnostic features of chronic pulmonary artery thrombosis are reviewed, and two additional cases are presented, in one of which the

diagnosis was made clinically and a surgical approach instituted, though unsuccessfully because of refractory cardiac arrest.

This unique form of cor pulmonale is characterized by increasing and progressive right-sided heart failure of variable duration. The final episode is related to increasing obstruction within the pulmonary artery which is not affected by any therapeutic medical regimen.

An awareness of the clinical syndrome prior to the terminal obstructive phase is essential, since it is in this interval that surgical therapy represents the most rational and hopeful approach to the removal of the mechanical block.

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Leptospirosis (Ballum) Contracted from Swiss Albino Mice

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Since the original isolation of the type species of Leptospira ballum from a mouse, Mus musculus spicilegus,[1] the natural occurrence of this serotype in colonies of Swiss albino mice has been demonstrated in Europe and the United States.[2,3] In addition, L. ballum has been recovered from house mice, Mus musculus, and an opossum, Didelphis virginiana, in Virginia[3]; from man and Norway rats, Rattus norwegicus, in Puerto Rico[4]; from Norway rats in British Columbia,[5] and from rice-field workers in France.[6]

Although the first diagnosed human infection was contracted from laboratory mice,[7] the handling of such infected mice had not been considered a serious health hazard for laboratory employees. The presence of L. ballum in mice in the breeding colony at the Rocky Mountain Laboratory was first demonstrated in 1949, but, until recently, human cases had not been recognized. In November, 1956, one member of the staff experienced a severe febrile illness that was complicated during convalescence by orchitis. After this illness was diagnosed as leptospirosis, a serologic survey of the laboratory staff was made to determine whether clinically similar syndromes previously observed among male employees also were attributable to leptospirosis. In this paper, the clinical aspects of four such cases are described and the health hazard associated with the handling of mice infected with L. ballum is discussed.

Materials and Methods

Since the agglutination-lysis test of Schuffner and Mochtar[8] detects antibodies for a longer period post infection than either the complement-fixation technique or the combination plate and capillary-tube test, the former was used for identifying past infections. Diagnosis of the recent case was based on results obtained with the combination plate and capillary-tube method[9] and the complement-fixation test.[10] A strain of L. ballum isolated from mice at this laboratory was used for the preparation of antigens employed in these tests.

Serums of laboratory personnel were obtained incidental to other studies made during 1955 and 1956. These serums were tested only against L. ballum, but serums positive against this serotype were examined also by the agglutination-lysis test for antibodies against L. canicola, L. icterohaemorrhagiae, L. pomona, L. hebdomadis, L. bataviae, L. grippotyphosa, L. autumnalis, L. pyrogenes, and L. sejroe.

Results

Of 58 persons who handled mice, 8 possessed antibody titers indicative of past infections with L. ballum, whereas 33 employees who did not contact mice in their work were serologically negative (Table 1).

TABLE 1.—*Prevalence of Antibodies Against L. Ballum Among Laboratory Personnel, According to Sex and Degree of Occupational Exposure*

Sex	Degree of Exposure *		
	None	Intermittent	Continuous
Male	0/22	3/25	5/28
Female	0/11	0/4	0/1
Totals	0/33	3/29	5/29

* Numerator indicates number of persons serologically positive at a dilution of 1:100 or greater on the agglutination-lysis test. Four of the eight positive serums possessed a lower titer of coagglutinins against L. canicola. Denominator denotes number or persons tested.

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Drs. R. L. Peterson and D. Gordon (deceased) provided clinical records of their respective patients.

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Four of the eight had experienced a severe febrile illness that was complicated during convalescence by complaints referable to the testes. Of the four remaining serologically positive men, two recalled severe, febrile, undiagnosed illnesses and two did not recall any unusual sickness. One serologically negative male disclosed a history of a febrile illness during November, 1951, accompanied by chills, sweats, headache, stiff neck, myalgia, nausea and vomiting, icterus, and hemoglobinuria; during a protracted convalescence he experienced pain and tenderness in the testes. This person was constantly exposed to infectious urine while he fed argasid ticks on the abdomens of mice. Possibly, he actually experienced leptospirosis in 1951, and serologic evidence of the infection is no longer detectable. The fact that 4 of 8 seropositive men had experienced a febrile illness followed by orchitis and only 1 of 67 seronegative men had been so affected strongly suggests an association of orchitis with leptospirosis ballum in man.

The clinical aspects of Case 1, a patient of one of us (D. M.), are described in detail. Since the clinical pattern and course of illness, including testicular involvement during convalescence, of three of the other serologically positive men were so strikingly similar to those of the proven case of leptospirosis, brief descriptions of their illnesses are also included. Information on these cases was obtained from attending physicians, from sick-leave records, and by personal interview of the patient.

The diagnosis of Case 1 was based on a rise in antibody titer between acute and convalescent specimens while only convalescent serums were available from the other three cases (Table 2). At the time these cases occurred, epidemiological evidence suggested that they were laboratory-acquired infections, but tests on acute and convalescent serums with Pasteurella tularensis, Brucella, Rickettsia prowazekii, R. rickettsii, Coxiella burnetii, and psittacosis antigens failed to demonstrate a rise in titer against these pathogens. Each of these patients had experienced mumps as a child, and at the time of their current illness their respective families were free of febrile illnesses.

Case 1.—A 43-year-old white man had been employed as a research bacteriologist since July 15, 1951. Since that date, he intermittently had close contact with Swiss albino mice; 15 days and 10 days prior to the onset of symptoms he had inoculated mice with Salmonella typhi. On Nov. 15, 1956, he rather suddenly became ill with weakness, malaise, chills, and fever. He was seen at home the next day and was found to have chills almost constantly and to be suffering from severe headache, weakness, and fever (temperature, 103 F). Physical examination was noncontributory. A tentative diagnosis of influenza was made, and oral fluids and acetylsalicylic acid were prescribed. The patient was not seen again until Nov. 19, and, since he had not improved, he was admitted to the hospital for further observation. Symptoms were continuing fever, chills, sweats,

Table 2.—*Serologic Findings on Four Described Cases of Leptospirosis Ballum*

Case and Date of Serum		Serotypes Used in Designated Tests †					
		L. ballum		L. canicola		L. pyrogenes	
	CF *	AL	P-CT	AL	P-CT	AL	P-CT
Case 1							
4/5/55	NT	0	0	0	0	0	0
11/19/56	0	100	0	0	0	160	0
12/6/56	64	5,000	640	100	40	100	0
1/9/57	2,048	500	160	100	0	100	0
Case 2							
1/9/57	NT	100	40	0	0	0	0
Case 3							
1/6/56	NT	100	40	0	0	0	0
Case 4							
3/4/55	NT	100	40	0	0	0	0
1/12/56	NT	100	10	0	0	0	0

* Complement-fixation test. NT indicates not tested.
† Other serotypes listed in methods did not react with serum dilutions greater than 1:10. AL indicates agglutination-lysis test; P-CT, plate capillary-tube test. Numbers are reciprocals of titers.

headache, general malaise, myalgia, prostration, and anorexia.

Examination on admission revealed an acutely ill white man who was so prostrated that even to give a history or turn over in bed was an effort. Temperature was 103.6 F orally; pulse rate was 90 per minute; blood pressure was 108 systolic, 70 diastolic; respirations were 24 per minute. Ocular fundi were normal. Pupils were equal, round, and regular and reacted to light. No conjunctival injection was noted. Ears, nose, and throat were normal; neck, supple; thyroid, not palpable; no lymphadenopathy. Chest was clear to percussion and auscultation, with equal expansion of both hemithoraces. The apex beat was within the midclavicular line. Sounds were of good quality; aortic second sound was greater than the pulmonic second sound; no thrills nor murmurs were present. Abdomen was soft, flat, and nontender; no organs nor masses were palpable. Genitalia were normal. Extremities were of normal size, shape, and range of motion. Peripheral pulses and deep and superficial reflexes were normal. Skin was celar.

Laboratory tests on day of admission revealed 3000 leukocytes per cubic millimeter and a differential smear which was normal in distribution and appearance. The following day laboratory findings were as follows: hemoglobin, 12.5 gm. per 100 ml. of blood; erythrocyte count, 3,800,000; leukocyte count, 3600, and again a normal differential smear. Urine was normal except for a 1+ albumin and 2+ sugar; however, urine had been taken after two infusions with dextrose. Results of repeated urinalyses on Nov. 21 and 23 were normal. On the latter date the following determinations were made: erythrocyte count, 3,820,000; hemoglobin, 11.9 gm. per 100 ml. of blood; white blood cell count, 5700, with normal differential smear; 4.5% sulfobromophthalein (Bromsulphalein) retention after 30 minutes.

Initially, he was treated with analgesics, sedatives, and parenteral fluids. Since the patient had been working with Salmonella, antibiotics were withheld pending results of cultures of blood and throat and rectal swabs. No bacterial pathogens were recovered from these specimens. On Nov. 21 (second hospital day), he was afebrile, but he suffered a recurrence of fever and severe headache during the night. The temperature was essentially normal thereafter, but headache and prostration persisted for the next two days. When discharged on Nov. 25 (seventh hospital day), he was afebrile but still weak. Other symptoms had regressed. Treatment had consisted solely of symptomatic and supportive measures. No antibiotics had been used.

He rested at home for a few days and tried to work on Dec. 4, but during the afternoon he felt chilled and that evening he developed pain and tenderness in both testes and had a recurrence of fever. On Dec. 7 he was found to have a marked rise in titer against L. ballum, but an attempt to isolate leptospirae by the inoculation of urine into hamsters failed. Erythromycin, 0.5 gm. immediately and 0.25 gm. every six hours, was taken for seven days (7.5 gm.). By Dec. 14, when the last dose of erythromycin had been taken, testicular tenderness had nearly subsided, but improvement had been slow. At this time the patient had started to regain the 8 lb. of weight lost during illness. He finally returned to work on Dec. 17, still weak, but otherwise asymptomatic.

CASE 2.—A 34-year-old white man had worked in the mouse-rearing colony since June 4, 1951. In his work he had daily contact with mice, and his hands were frequently contaminated with mouse urine. On Sept. 16, 1954, he developed an illness characterized by a dull bilateral headache, backache, myalgia, nausea, anorexia, and fever (temperature, 104 F). During the night he experienced chills and sweats. He was seen by his family physician on Sept. 17, at which time oxytetracycline was prescribed. His temperature returned to normal within 24 hours, but anorexia, severe headache, and malaise persisted. On Sept. 23, he was again seen by his physician. At this time laboratory tests revealed a leukocyte count of 8800 per cubic millimeter and results of tests for urinary albumin and sugar were negative. Five days later the patient experienced a febrile relapse accompanied by an intense headache. Hematologic studies performed during the relapse revealed leukocyte counts of 10,800 and 17,500, respectively, on Sept. 28 and 30. Treatment with chloramphenicol was initiated on the latter date. Symptoms subsided gradually, and the patient returned to work 11 days later. On Oct. 14 he complained of severe and persistent pain in both testes and a low-grade fever (temperature, 99 to 102 F). No swelling was evident, but the testes were particularly tender on palpation. Symptoms of orchitis had subsided by the sixth day, but on the following day pain and tenderness reappeared. The second attack of orchitis was severer than the first, and it persisted until Oct. 28, 1954. Convalescence was slow, and the patient became fatigued readily during the subsequent three to four weeks.

CASE 3.—A 42-year-old white man had been employed at this laboratory since July 14, 1949. The type of work he performed was similar to that of Case 1. On Feb. 15, 1951, he became ill with fever (temperature, 102 to 104 F), mild headache, chills, and drenching sweats. Physical examination by his attending physician on the following day was noncontributory. Leukocyte count determined during this visit was 6000 per cubic millimeter. Results of heterophil antibody and

Wassermann tests performed with serum taken Feb. 18 were negative. Penicillin was administered on Feb. 16 and 17, and the patient became asymptomatic within 48 hours. On Feb. 21 and 22 he experienced a febrile relapse from which he recovered spontaneously. The following week the patient returned to work, but he became fatigued easily. On March 10 he complained of slight swelling, pain, and tenderness in the right testicle. Chloramphenicol was administered, but symptoms persisted and gradually abated by the seventh day. After the right testis returned to normal, the left side was affected for about a week. During the subsequent two to three weeks of convalescence the patient tired easily.

CASE 4.—A 31-year-old white man had been employed at this laboratory since June 27, 1954. Among his duties were the feeding of argasid ticks on the abdomens of rabbits and the inoculation of mice with P. pestis. On July 16, 1954, he suddenly became ill with high fever (temperature, 105 F), violent chills, sweats, and extreme weakness. Two days later he was examined by his physician, and treatment with chloramphenicol was instituted. During illness, excretion of urine was apparently decreased; the patient recalled intervals of retention as long as 36 hours. Fever dropped by lysis by the eighth day. On Aug. 3, 1954, he experienced pain and tenderness in both testes, accompanied by low-grade fever (temperature, 100 F). Spontaneous recovery occurred in three days. Seven days later symptoms of orchitis and low-grade fever recurred and persisted for two days. The patient was weak and became fatigued easily during the subsequent two months.

After the patient had recovered, he disclosed that he had been bitten by three ticks, Ornithodoros moubata, that possibly may have been infected with the spirochete, Borrelia duttonii. Since a diagnosis of this disease can be made satisfactorily only during the febrile period, it was impossible to ascertain whether his illness was relapsing fever. However, the course of this illness was entirely dissimilar to that of an infection with B. duttonii. This type of relapsing fever is characterized by an initial fever of two to three days which drops by crisis; thereafter, the patient usually experiences three to four febrile relapses of similar character and duration. Since, in the present case, the initial fever persisted for eight days and dropped by lysis and since orchitis occurred during convalescence, this case was probably leptospirosis.

Comment

Since 8 of 58 employees who had close contact with mice experienced leptospirosis, infected mice apparently cannot be handled with impunity. Of the four cases described, Case 4 contracted the disease shortly after his initial contact, whereas the other three persons had handled infected mice for two to five years. The actual mode of infection in these cases is unknown, but possibly skin abrasions were contaminated with mouse urine. The presence of L. ballum in mice in the breeding colony at this laboratory was first recognized in 1949. About 80% of the mature breeding females are infected and persistently shed leptospirae in their urine. Since men working in the rearing colony and technicians inoculating mice frequently contaminate their hands with infectious urine, it is surprising that more cases had not occurred, but, presumably, L. ballum does not readily penetrate the unbroken skin.

Recent isolates of L. ballum from mice at this laboratory regularly kill young guinea pigs and hamsters. Although no fatal human cases occurred, a high percentage of seropositive persons had suffered a severe febrile debilitating illness; two of the affected employees were incapacitated for more than a month.

Although the clinical patterns of these four cases were similar, no group of signs or symptoms was sufficiently characteristic that leptospirosis was suspected at the time of illness. Only one patient developed a leukocytosis ordinarily associated with leptospirosis. All suffered high fever accompanied by chills and sweats. Prostration and malaise were prominent symptoms. Two were affected with severe headaches and generalized myalgia. All had symptoms of testicular involvement which developed 10 to 16 days after the febrile illness. One complained of persistent pain in his testes, whereas the other three complained chiefly of tenderness on palpation and pain on movement; relief could be obtained by sitting or reclining quietly. In contrast to mumps orchitis, little or no swelling occurred in these cases, and the testes remained normal in size after spontaneous recovery.

Summary

At the Rocky Mountain Laboratory, 8 of 58 employees who had close contact with infected Swiss albino mice were serologically positive against Leptospira ballum, whereas 33 persons who did not contact mice in their work was negative. Case histories of four patients whose febrile illnesses were associated with subsequent testicular involvement are presented. The presence of L. ballum in a colony of Swiss albino mice is considered a serious health hazard to personnel who handle mice during rearing operations and biologic research.

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The Unilateral Nonfunctioning Kidney

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Intravenous pyelography is often utilized as a diagnostic aid to help clarify many different clinical problems. When both kidneys are visualized by this technique many problems can be solved. Occasionally one side will fail to concentrate the urographic medium. When this situation is found some interesting questions arise: 1. Why did one side fail to concentrate the media? 2. What further examinations are necessary to make the diagnosis? 3. What should be looked for in making the diagnosis? To help clarify the problem of differential diagnosis a series of such cases was reviewed. Seventy cases from the Seattle Veterans' Administration Hospital, King County Hospital, and the Children's Orthopedic Hospital were collected and reviewed. No attempt was made to establish the incidence of this problem.

The cases were divided into three groups: (1) primary diseases of the genitourinary tract, (2) diseases in which the diagnosis is not completely certain or has not been established by tissue examination, (3) diseases secondarily involving the genitourinary tract. The established diagnosis and the average age of the patients are shown in Table 1. The symptoms and signs of illness for the patients in Group I are summarized in Table 2.

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TABLE 1.—*Established Diagnosis and Average Age in Seventy Cases*

Diagnosis	Pts. No.	Average Age
Group I—Primary disease of the genitourinary tract	40	
Nephrolithiasis	12	58
Carcinoma of the kidney	8	66
Carcinoma of the bladder	5	60
Congenital	4	27
Pyelonephritis	4	65
Renal artery thrombosis	3	55
Tuberculosis	2	31
Renal artery aneurysm	1	36
Surgery	1	39
Group II—Etiology uncertain, suspected diagnoses	18	
Renal artery thrombosis	3	58
Pyelonephritis	2	74
Tuberculosis	2	60
Congenital	5	42
Incomplete study	5	58
Trauma	1	35
Group III—Diseases secondarily involving the genitourinary tract	12	
Carcinoma of the cervix	7	48
Carcinoma of the colon	3	72
Ovarian neoplasms	2	41

Group I—Primary Diseases of the Genitourinary Tract (Forty Cases)

Nephrolithiasis (Twelve Cases).—Eight of the patients in this group gave a definite history of renal colic. Two of the patients had gross hematuria. Three of the group had calculi discovered incidentally and gave no history of disease involving the urinary tract. The only helpful physical finding was tenderness to palpation in the costovertebral angle, which was present in nine of the cases. Only five of the cases had demon-

TABLE 2.—*Symptoms and Signs of Illness*

	Renal Stone	Renal Ca	Bladder Ca	Congenital	Pyelo-nephritis	Renal Art. Thrombosis	TB
Pain	8	4	1	2	1	1	1
Hematuria	2	4	5		1		
Dysuria, frequency, and urgency	3	1	1	1	3		1
Polyuria					1		
Nocturia					1		1
Poor stream	1						
Anorexia, weight loss		2	2			1	
Previous history of stones	2	1					
Previous history of bladder tumor			3				
Mass		1		2			

strable hematuria. In each instance a radiopaque calculus was demonstrated at the site of obstruction.

Six of the group had nephrectomies performed, two for staghorn calculi and the remainder for complicating hydronephrosis and pyelonephritis. Two patients passed the stones spontaneously. In two cases the stones were removed surgically. Two patients were poor surgical risks and were treated conservatively.

Carcinoma of the Kidney (Eight Cases).

Three patients entered complaining of pain and hematuria; one, of pain alone. One patient had symptoms of a urinary tract infection. Two patients noted anorexia, weight loss, and fatigability. The most significant physical finding in five of the cases was the presence of a palpable flank mass. Two of the patients had microscopic hematuria. In two cases flank mass was noted on the plain x-ray film of the abdomen.

In each of the cases in which a successful retrograde pyelogram was performed a mass was demonstrated. One patient with a transitional-cell carcinoma of the renal pelvis had tumor implants about the ureteral orifice (Fig. 1). One patient had metastases to the lung, another to the lumbar spine, which further confirmed the clinical impression. Three of the cases were inoperable. The remainder of the cases underwent successful nephrectomies.

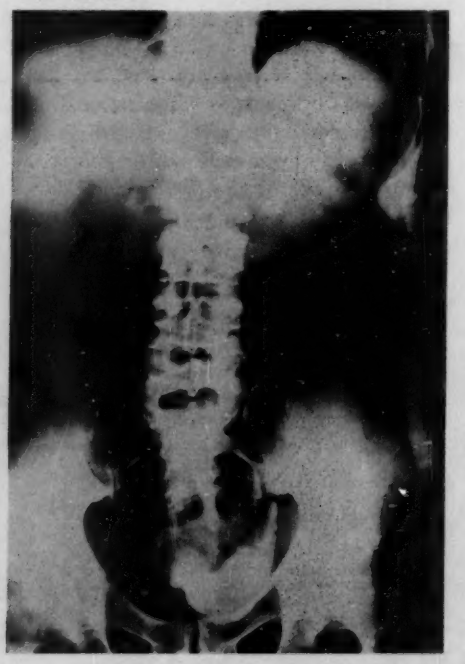
Fig. 1.—Retrograde pyelogram, showing dilatation of the left ureter and marked irregularity of the ureter and pelvis.

Carcinoma of the Bladder (Five Cases).

Each of the cases in this group had gross hematuria prior to admission to the hospital. In one case a nonfunctioning kidney plus a markedly deformed bladder suggested the diagnosis of carcinoma of the bladder obstructing the ureter (Fig. 2). The diagnosis was easily established in each case by cystoscopy.

Congenital (Four Cases).—The four cases in which the diagnosis was substantiated consist of two cases of hydronephrosis, a case of agenesis of the kidney, and a case of multicystic kidney. In both cases of hydronephrosis the clinical impression was verified by retrograde pyelography and the etiology of the obstruction determined by surgical exploration. One patient with an aberrant

Fig. 2.—Intravenous pyelogram, demonstrating a nonfunctioning right kidney and marked distortion of the bladder.



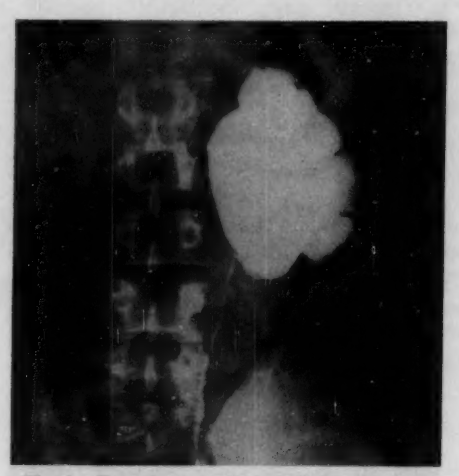


Fig. 3.—Retrograde pyelogram, demonstrating an obstruction at the ureteropelvic junction with a marked hydronephrosis.

renal artery (Fig. 3) obstructing the ureteropelvic junction complained of loin pain and gave a history of recurrent kidney infection. The second patient had bilateral apparently congenital strictures at the ureteropelvic junction. This patient's complaints were pain in the flank and a palpable mass on the same side.

The patient with agenesis entered the hospital complaining of a vaginal discharge. Physical examination revealed a bicornuate uterus. At cystoscopy the right ureteral orifice was found to be absent. Surgical exploration was performed, and no renal tissue was found. The case of multicystic kidney occurred in a 2½-year-old boy with marked abdominal swelling. The true nature of the mass causing the swelling was determined only by pathologic examination of the surgical specimen.

Pyelonephritis (Four Cases).—A history of frequency, dysuria, and urgency led to the discovery of a nonfunctioning kidney in three of the cases. All of these cases were normotensive, and the physical examination was normal. Pyuria and a positive urine culture were found in each case. One patient was found to have dilated calyces upon retrograde pyelography. The second patient was noted to have an amorphous mass of calcium in the region of the nonfunctioning kidney. The third patient had no visible ureteral orifice, so retrograde pyelography was impossible. Percutaneous anterograde pyelography was performed, and a small irregular multilobulated sac-like structure was seen. The fourth patient was a 60-year-old white man with severe hypertension who had been known to be normotensive two years ago. The patient's blood pressure was 240/120, and severe retinal changes were noted. An intravenous pyelogram showed no visualization of the right kidney. Retrograde pyelography revealed a normal kidney pelvis and calyces. No urine or indigo carmine was recovered from the kidney. An aortogram did not visualize the renal artery on the affected side. The diagnosis of renal artery thrombosis was made and a nephrectomy performed. At the time of surgery renal artery thrombosis was not found. The kidney weighed 63 gm. The pathologic diagnosis was atrophic pyelonephritis. Following the procedure the patient had a marked drop in both the systolic and the diastolic pressures to normotensive levels.

Renal Artery Thrombosis (Three Cases).

One of the patients in this group had the nonfunctioning kidney discovered during an investigation of hypertension. The patient denied symptoms referable to the genitourinary tract. The patient subsequently died of a carcinoma of the lung. At autopsy a renal artery thrombosis was found.

The second patient developed thrombosis secondary to an aortogram which was performed for occlusive arterial disease. Two days after aortography a plain x-ray of the abdomen showed opacification of one kidney. No medium was visualized in this kidney when intravenous pyelography was performed. The patient died following surgery for relief of the occlusive arterial disease. At autopsy the entire kidney was infarcted secondary to thrombosis of the renal artery.

The third case is of sufficient interest to present in more detail.

This was the second hospital admission for this 37-year-old white man. The patient entered with the chief complaint of a dull constant pain local-

ized in the right upper quadrant of the abdomen. The pain had been present for five days and had increased in severity. Five years previously the patient had been hospitalized and treated medically for a possible perinephric abscess on the same side. Significant physical findings included hypertension, with blood pressure of 180/105; temperature, 101.8 F; pulse, 120 per minute. There was voluntary guarding, with mild right-upper-quadrant and right-costovertebral-angle tenderness. The bowel tones were hypoactive. The findings on urinalysis were persistent proteinuria and microscopic hematuria. The hematocrit was initially 54%, later dropping to 42%. The initial blood urea nitrogen was 21 mg. per 100 cc., later dropping to 17 mg. per 100 cc. A nonfunctioning right kidney was discovered by intravenous pyelography. A kidney of normal architecture which failed to excrete urine and indigo carmine was noted on retrograde pyelography. Four days after admission the patient had two generalized convulsive seizures. The blood pressure was 210/152 shortly after the seizures. The patient was given hypotensive drugs until a nephrectomy was performed. After surgery the patient's blood pressure rapidly returned to normal levels. A complete occlusion of the right renal artery secondary to a hemorrhage into the wall of the renal artery was found. The pathological interpretation was cystic medial necrosis of the renal artery, with intramural hemorrhage.

Tuberculosis (Two Cases).—The possibility of renal tuberculosis in these two cases was easily suspected by history. One patient had a history of tuberculous epididymitis several years ago. This patient entered with symptoms of flank pain and intermittent dysuria. The other patient had a definite history of tuberculosis in the family. This patient had symptoms of infection as well as microscopic hematuria. Acid-fast bacilli were not demonstrated either by smear or by culture of the urine in either case.

The patient with the history of tuberculous epididymitis had no visible ureteral orifice on the nonvisualized side. A retroperitoneal air study was performed, and the presence of the kidney was verified (Fig. 4). The organisms were seen in the removed kidney, which had been completely destroyed by the tuberculous process. The lower ureter had been obliterated by infection and stricture.

Fig. 4.—Retroperitoneal air study, demonstrating the definite presence of a left kidney.

Cystoscopy and retrograde pyelography were of more help in the second case. The ureter on the affected side was irregular and constricted, suggesting ureteritis secondary to tuberculosis. The acid-fast bacilli were demonstrated in the tissue sections of the removed kidney.

Surgical Division of a Ureter (One Case).

A 39-year-old Negro woman entered the hospital with symptoms of a ruptured tubal pregnancy. A total hysterectomy and bilateral salpingo-oophorectomy were performed for an ectopic pregnancy of the left broad ligament. The patient had a very stormy postoperative course. An intravenous pyelogram performed in the postoperative period revealed no concentration of dye in the left kidney. Retrograde pyelography demonstrated that the ureter had been divided in its lower third. The ureter had been divided at the time of surgery and not recognized.

Renal Artery Aneurysm(?) (One Case.)—This patient was a 36-year-old white man who was subject to recurrent bouts of abdominal pain of undetermined etiology. The

patient was known to be hypertensive. He had been hospitalized twice in the past for abdominal pain. During one of these episodes an appendectomy was performed and a normal appendix found. An intravenous pyelogram was then performed and a nonfunctioning kidney found. A kidney with normal architecture which failed to excrete urine and indigo carmine was demonstrated by retrograde pyelography. At exploration a pulsating mass was found in the renal artery near its origin. It was the impression of the surgeon that this mass represented an aneurysm of the renal artery and not poststenotic dilatation. A nephrectomy was performed. A pathologic diagnosis of membranous glomerulitis without necrosis was made. The patient sustained a reduction of his blood pressure to near normal levels.

Group II—Etiology Undetermined (Eighteen Cases)

All cases in which the diagnosis was not conclusively proved were placed in this group. These cases are subdivided into the following probable diagnoses.

Renal Artery Thrombosis (Three Cases). Each patient was severely hypertensive. The nonfunctioning kidney was discovered during the course of investigation for hypertension. The diagnosis was suspected by the following findings: (1) normal ureter and pelvis, (2) normal-sized kidney, (3) no urine or indigo-carmine excretion. As shall be discussed, these findings do not always make the diagnosis.

Chronic Pyelonephritis (Two Cases).—The clinical diagnosis of chronic pyelonephritis was made in two cases by the retrograde pyelographic findings of a small contracted kidney with blunting of the calyces. One of these cases had a definite history of infection in the past. Both of these cases had positive urine cultures.

Congenital (Five Cases).—One patient was diagnosed as having polycystic kidneys. The diagnosis was based upon the following findings: (1) age, 42; (2) 25-year history of hypertension; (3) a palpable kidney; (4) urine of low specific gravity; (5) proteinuria; (6) elevated creatinine; (7) functioning kidney showing, by intravenous pyelography, multiple filling defects spreading the calyces.

In the four cases in which agenesis of the kidney was suspected, the patients' admission complaints were not referable to the genitourinary tract. The nonfunctioning kidney was discovered incidentally in the course of the patients' investigation. Three of the patients had hypoplastic trigones and absent ureteral orifices. One patient had a normal trigone but an absent ureteral orifice. In this patient no renal shadow was seen on retroperitoneal air study.

Tuberculosis (Two Cases).—The diagnosis of tuberculosis was suggested in two cases. The occurrence of abacterial pyuria, hematuria, and flank pain in a patient with positive pulmonary lesions is certainly suggestive. Bilateral ureterovesical obstruction with hydroureter was seen on retrograde pyelography. In another patient, a 71-year-old white woman, a perinephric abscess drained spontaneously. On that side no renal function was demonstrated by intravenous pyelography. By retrograde pyelography an irregular ureter and renal pelvis were demonstrated. Repeated cultures of the urine and the draining material failed to demonstrate bacteria, fungi, or acid-fast bacilli. Therefore, a definitive diagnosis cannot be made.

Trauma (One Case).—A 35-year-old white man entered the hospital with the history of hematuria 12 hours after a back injury. The left kidney was not visualized by intravenous pyelography. Marked enlargement of the lower pole of the kidney with marked displacement of the ureter was demonstrated by retrograde pyelography. Surgery was refused, so the exact etiology will remain in doubt.

No Diagnosis (Five Cases).—In five cases no clinical diagnosis was made. All five patients had genitourinary tract symptoms. The symptoms were either those of infections (in three patients) or pain (in

two patients). In only one case was a successful retrograde pyelogram performed, and it was normal. It is obvious that without some visualization of the involved kidney no reasonable diagnosis can be made.

Group III—Diseases Secondarily Involving the Genitourinary Tract (Twelve Cases)

The diagnosis of carcinoma of the cervix at the stage in which obstruction of the ureters occurs is rarely difficult. An adequate pelvic examination followed by a biopsy will make the diagnosis. All of the cases in this group were League of Nations, Stage IV. The diagnosis had been established prior to this and definitive therapy initiated in each case. Each of the seven patients in this group had received radiation.

In three cases a recurrent carcinoma of the left colon (two sigmoid, one rectum) had obstructed the ureter on one side. Retrograde pyelography had established the diagnosis in each case.

In two cases ovarian neoplasms were responsible for the ureteral obstruction and nonfunction. One of these was a benign cystadenoma in a 16-year-old girl. The patient entered with a history of abdominal swelling. The pyelogram was performed prior to surgery. After the tumor was removed the patient's renal function on the affected side returned to normal. The second patient, a 67-year-old white woman, had deep x-ray therapy for an inoperable carcinoma of the ovary two years prior to admission. Retrograde pyelography demonstrated the obstruction of the ureter by residual tumor.

Comment

It is obvious from the foregoing presentation that a satisfactory diagnosis can be established in the majority of cases in which a nonfunctioning kidney is discovered.

Nephrolithiasis should rarely present great difficulties in diagnosis if the following are used as indications for intravenous pyelography: (1) a history of abdominal pain suggestive of renal colic, (2) hematuria, (3) urinary tract infection, (4) any previous history of nephrolithiasis. The nonopaque calculus must always be kept in mind when considering this diagnosis. Higgins,[1] in a review of the literature, cites the incidence of nonopaque stones to range from 2% to 16.5%.

When a carcinoma of the kidney results in a nonfunctioning kidney the problem of diagnosis is usually made more difficult. In this series of cases the diagnosis was fairly easy, but situations are reported in the literature[2-4] in which the diagnosis of renal neoplasm in a nonfunctioning kidney cannot be established by the routine urologic procedures. Aortography has proved valuable in these cases. Palmlöv[2] describes two phases of filling, the arterial phase and the nephrographic phase. During the arterial phase, irregular vessels are seen within the tumor itself. In the nephrographic phase, contrast medium is seen pooling within the sinus spaces of the tumor.

Since hematuria occurs so frequently with bladder tumors, the diagnosis should rarely be missed if the usual urologic routine is followed. The intravenous pyelogram followed by cystoscopy will establish the diagnosis and location of the tumor.

The clinical evaluation of a unilateral small kidney is very difficult. Emmett et al.[5] reviewed a group of small kidneys (by definition, less than two-thirds normal size or less than 100 gm. by weight) to determine if there were any methods clinically or pathologically to separate the atrophic pyelonephritis from congenital hypoplasia. Their study indicated it was impractical and almost impossible to distinguish, either clinically or pathologically, between hypoplasia and atrophic pyelonephritis. The conclusion reached was that it might be more practical to employ a term such as "atrophic kidney" or "renal atrophy" to describe the unilateral small kidney, the cause of which is not apparent.

In recent years reports of renal infarction have become commoner.[6-11] The cause of

renal infarction is arterial or venous occlusion secondary to embolism, thrombosis, or trauma. Of 94 cases reviewed by Regan,[8] 71 were arterial, 20 were venous, and 3 were traumatic in origin. Emboli are the commonest cause of infarction to the kidney. Seventy-six to ninety-five per cent of patients with arterial emboli have heart disease.[9] The remainder of the cases were spontaneous thrombosis of the renal artery, presumably by hemorrhage into an atheromatous plaque. With emboli, the entire kidney is rarely infarcted, so most of the renal function is preserved. If complete occlusion occurs, function ceases and nonvisualization by intravenous pyelography occurs. The patient may note back pain and/or hematuria, but many times no history of symptoms is available. The cases with complete occlusion are usually discovered either by a fortuitous intravenous pyelogram or at autopsy. If on retrograde pyelography the following are noted, the diagnosis is usually renal artery thrombosis: (1) a normal-sized kidney, (2) a normal renal pelvis and calyceal system, (3) no urine excreted, (4) no indigo carmine recovered. Later the kidney will become atrophic and the diagnosis will be established only by pathologic examination of the kidney. The aortogram may suggest the diagnosis by establishing that there is no flow of dye through the renal artery, but technical limitations do not always lead one to accept failure of visualization as evidence of occlusion.

It must be remembered that renal infarction can be produced by aortography. Injection of the radiographic dye directly into one or both renal arteries can result in loss of renal function.[12]

Venous thrombosis usually occurs with septic states and is often bilateral. Initially the kidney is much larger than normal. Retrograde pyelography shows a deformity and incomplete filling of the pelvis and calyceal system. If the kidney is not removed, the thrombus will usually propagate and lead to a fatality. If the patient survives, the kidney will atrophy.[8]

The diagnosis of renal infarction secondary to trauma is usually easy if the history of injury and hematuria are followed by an intravenous pyelogram.[6,10,13] An interesting sequel which must always be kept in mind is the development of severe hypertension.[10] The hypertension which develops is often relieved by nephrectomy. The types of congenital lesions which commonly result in nonvisualization of one kidney by intravenous pyelography are (1) renal agenesis; (2) renal aplasia; (3) renal hypoplasia; (4) hydronephrosis secondary to aberrant vessel, congenital stricture, etc.; (5) unilateral multicystic kidney; (6) ectopic ureter.

Nation[14] separated renal agenesis from aplasia. With aplasia there is some vestige of the renal anlage present, and it is the result of failure of fusion of the ureter and the nephrogenic cap. Renal agenesis results from the failure of the metanephric blastema to develop. With aplasia there is usually a ureteral orifice and corresponding half of the trigone, but this is not invariable. Absence of the ureteral orifice and corresponding side of the trigone is strong evidence of renal agenesis.[15] If the ureter is present, it usually terminates at or near the bladder. In some cases there are no reliable methods of separating them clinically.

Longo[16] reviewed 94 cases of congenital solitary kidney and found that only 11 had no genitourinary tract symptoms and signs. Pain and symptoms of infection were the most commonly encountered. The solitary kidney may be palpable in 25% of the cases. Associated congenital anomalies are commonly found (in males, 30%; in females, 54% of cases). The anomalies most commonly seen involve the genital tract on the side of the absent kidney.

If no ureter is visible but the trigone is present, a retroperitoneal air study or aortography may demonstrate the presence or absence of a kidney.

The differential diagnosis between hypoplasia and agenesis or aplasia should present no problems, since there is an intact ureter attached to the kidney with hypoplasia.

When hydronephrosis secondary to a congenital defect occurs the patient will usually give a history of pain and/or infection.[17] The presence of flank tenderness and a palpable mass suggest the diagnosis. It is usually not difficult to establish the presence of hydronephrosis by retrograde pyelography, but many times it is difficult to establish the etiology of the obstruction. Casey and Goodwin [18] have injected dye percutaneously into the dilated renal pelvis and found it to be of value in establishing the etiology of the hydronephrosis. Palmlöv [2] has successfully demonstrated by aortography the presence of an aberrant renal artery as the cause of obstruction at the ureteropelvic junction.

Spence [19] described unilateral multicystic disease, contrasting it from polycystic disease and other cystic diseases of the kidney. In this instance the entire kidney is replaced by many cysts, which are held together by loose connective tissue. Clinically there is often a palpable mass. There is no function by intravenous pyelography. The ureter is either absent or ends in a blind termination near the ureteropelvic junction. Pathologically there are no recognizable nephrons present. Since visualization of the kidney cannot be performed by retrograde pyelography, other means must be utilized to make the diagnosis. Aortography and retroperitoneal air study may well provide the necessary information to at least suspect the diagnosis. Finally, however, the diagnosis can only be established by pathologic examination of the kidney.

The diagnosis of tuberculosis of the genitourinary tract cannot be established without the demonstration of the acid-fast bacillus. The history is often suggestive, and the symptoms are usually those of infection. Although not a common cause of the nonfunctioning kidney, it must always be kept in mind.

Renal artery aneurysm is a rare and interesting lesion. Abeshouse [20] reviewed the literature and found that the clinical diagnosis had been made in only 35 of 113 cases. When present there are certain features which help substantiate the diagnosis. Some of the diagnostic features are (1) palpable mass, (2) the presence of a thrill and bruit, (3) presence of a calcified mass in the region of the renal artery found by x-ray. None of the above features were present in the case in this series. The diagnosis could only have been made if other studies, such as an aortogram, had been performed prior to surgery.

Neoplastic diseases other than those of the genitourinary tract may obstruct the ureter and result in a nonfunctioning kidney. Of our 13 cases, 11 were malignant tumors. With the carcinomas of the colon, the obstruction was in each instance produced by local recurrent tumor. A retrograde pyelogram is the simplest way of demonstrating whether or not the urinary tract is obstructed by tumor.

A cause of the nonfunctioning kidney in the postoperative period is unrecognized surgical division or ligation of the ureter. Aschner [21] presented data on 15 cases in which ureteral injury was produced. Unilateral injury occurred in 11 cases. Three kidneys were removed by nephrectomy, one atrophied in situ. Aschner [21] stressed the use of ureteral catheters for identification of the ureter and prevention of injury. If abdominal complaints persist after surgery and flank pain or ureteral pain appears, the possibility of ureteral injury must be considered. If injury is suspected, intravenous pyelography will support it; cystoscopy and indigo-carmine-excretion studies will establish the diagnosis.

Summary and Conclusions

From this study of 70 cases of unilateral nonvisualization of a kidney by intravenous pyelography and a pertinent review of the literature the following points can be made:

1. Extrarenal lesions which occasionally result in nonvisualization of one kidney are readily diagnosed by the combination of plain x-ray film of the abdomen, cystoscopy, and retrograde pyelography.

2. Disease of the kidney parenchyma, whether congenital or acquired, will present the greatest problems in diagnosis. (*a*) A kidney of normal size and architecture without function suggests renal artery thrombosis. (*b*) A kidney of small size with normal architecture without function suggests hypoplasia or renal artery thrombosis. (*c*) A small kidney with abnormal architecture without function suggests atrophic pyelonephritis or hypoplasia. (*d*) Aplasia or agenesis is suggested if the ureteral orifice is missing either alone or in combination with an absent trigone. (*e*) Ectopic implantation of the ureter and inflammatory obliteration of the ureter must be kept in mind when the ureteral orifice alone is not seen. (*f*) Retrograde pyelography will usually confirm the diagnosis of neoplasms, tuberculosis, and congenital malformation of the pelvis and ureter. (*g*) Aortography may aid in the diagnosis of neoplasms, renal artery thrombosis, aberrant renal artery, and agenesis.

3. Neoplastic disease of the colon and female reproductive tract may result in nonvisualization of one kidney by extraluminal obstruction of ureter.

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Congenital Biologic False-Positive Serologic Test for Syphilis

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Since Wassermann and his associates introduced serologic methods in the diagnosis of syphilis shortly after the etiological agent was discovered by Schaudinn and Hoffmann, in 1905, many problems have become apparent in making a correct, specific diagnosis. The use of penicillin in the treatment of syphilis by Mahoney and his associates, in 1943, revolutionized the clinical management of the disease. Now it frequently takes longer to make a correct diagnosis of a case than to cure it. The very effective use of penicillin has been a mixed blessing, since its ease of administration has decreased the diligence of the physician in his pursuit of a correct diagnosis before instituting treatment. Some patients have suffered psychic trauma by the diagnosis and treatment of nonexistent disease carrying social stigma.

The speed and simplicity of treatment with penicillin has changed the diagnosis and treatment from clinic care to the private physician's office. It is here the diagnosis should be made, if possible, before treatment is instituted.

The problem of the biologic false-positive test for syphilis has become increasingly important since the introduction of specific tests. Biologic false-positive reactions are frequently observed in patients with vaccinia, infectious mononucleosis, malaria, leprosy, upper respiratory diseases, yaws, pinta, Colorado tick fever, relapsing fever, lymphogranuloma venereum, chancroid, measles, chickenpox, atypical pneumonia, infectious hepatitis, rat-bite fever, and disseminated lupus erythematosus. In fact, any febrile illness or immunization is a potential cause of false-positive tests.

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No patient who has recently had a febrile illness or immunization should be diagnosed as having syphilis on the basis of serologic tests alone. A false-positive serologic test should be considered in all patients without a history or clinical evidence of syphilis. It should be considered in persons whose marital partners have negative serologic reactions.

In all patients where there is a possibility of a false-positive serologic test a careful history should be taken as to exposure, symptoms of intercurrent infection, and immunization, and a physical examination should be done for evidence of other etiologic factors. Appropriate tests should be taken to determine the presence of other diseases. Repeated serologic tests should be taken with use of different techniques in different laboratories. Periodic tests should be taken as the reactions change in the false-positive serologic tests. The so-called provocative tests are of no value in the diagnosis of questionable reactions.

The cause of a false-positive reaction cannot always be determined. It is in this group that one should consider the possibility of a congenital biologic false-positive reaction.

The present family study demonstrates an example of the problems involved in making a correct diagnosis and thus avoiding psychic injury to the patient by treating a nonexistent disease which unfortunately carries social considerations. It also avoids the complications of treatment with penicillin, which now occur in about 5% of the hospital-treated patients.

Case 1	Case 2
Female, age 59	Male, age 61
Married, 5 children Medical history Diphtheria Diabetes Mellitus Physical examination Hypertension	Married, 5 children Medical history Normal Physical examination Normal
Blood studies Blood group O, Rh + Total protein 8.0 Alb. 4.4 Glob. 3.6 A/G ratio 1.2	Blood studies Blood group A, Rh + Total protein 9.0 Alb. 4.0 Glob. 5.0 A/G ratio 0.8

Case 3	Case 4	Case 5	Case 6	Case 7
Female, age 36	Male, age 34	Male, age 32	Female, age 29	Female, age 27
Married, 3 children Medical history Appendectomy	Married, 4 children Medical history Appendectomy T. and A.	Married, 4 children Medical history Spinal fusion Vein ligation "Kidney stone"	Married, 2 children Medical history Nephritis	Married, One miscarriage Medical history Pneumonia, T and A. Bilateral herniaplasty, Benign Fallopian tumor
Physical examination Normal	Physical examination Normal	Physical examination Normal	Physical examination Normal	Physical examination Normal
Blood studies Blood group A, Rh + Total protein 8.4 Alb. 4.4 Glob. 4.0 A/G ratio 1.1	Blood studies Blood group AB, Rh + Total protein 8.3 Alb. 4.1 Glob. 4.2 A/G ratio 1.	Blood studies Blood group A, Rh + Total protein 7.1 Alb. 3.5 Glob. 3.6 A/G ratio 1.	Blood studies Blood group O, Rh + Total protein 7.1 Alb. 3.7 Glob. 3.4 A/G ratio 1.3	Blood studies Blood group O, Rh + Total protein 8.5 Alb. 4.2 Glob. 4.3 A/G ratio 0.9

All blood counts and electrophoretic protein patterns were normal

A brief outline of the family and the tests done are presented in the Figure and the Table.

It is noted that only the females of the family exhibit the positive reactions (Cases 1, 3, 6, 7). The positive tests are of low titer and are negative in some instances (Cases 1, 3). The T. P. C. F. test was reactive in one case (Case 3) on two examinations in which the serological tests were negative. The T. P. I. was always nonreactive.

Results of Tests

Test	Case 1			2		3			4	5		6			7		
	1/54	4/54	5/57	1/54	5/57	2/54	4/57	5/57	4/57	2/54	4/57	10/53	11/53	5/57	2/54	4/57	5/57
V. D. R. L.	+	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+
Kahn	+	−	−	−	−	−	+	−	−	−	−	+++	+++	++++	+++	++	++
Hinton	+	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+
Kolmer	−	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+
T. P. C. F.			Nonreactive −		Nonreactive −		Reactive +	Reactive +	Nonreactive −		Nonreactive −			Nonreactive −		Nonreactive −	Nonreactive −
T. P. I.			Nonreactive −				Nonreactive −	Nonreactive −									Nonreactive −

The male members of the family showed consistently negative tests.

Summary of Observations

A family is presented with a biological false-positive test for syphilis. Although the size of the family and the number studied are too small to draw conclusions as to the hereditary pattern or type of transmission, it is noted that all the positive members are females and that the males are consistently negative. The positive reactions are of low titer. The test results vary from time to time in the members who show a positive reaction.

The T. P. C. F. test may be positive in female members whose serology is negative. The T. P. I. is indicated where the T. P. C. F. is positive. It proved to be consistently nonreactive in this family.

The electrophoretic study shows a normal protein distribution pattern. The T. P. I. bears out the clinical conclusion of a congenital biologic false-positive serologic test.

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The Acute Effect of Acetylsalicylic Acid in Man

On the Plasma Concentration of Corticoids, the Corticotropin (ACTH) Response, and Urinary Steroid Excretion

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Acetylsalicylic acid (ASA) is efficacious, as are adrenocortical steroids, in the treatment of acute rheumatic fever.[1,2] Similarity in the symptomatic relief produced by ASA and by cortisone in arthritic patients suggests a similarity of action.[3,4] That some interrelation may exist has been proposed by several investigators.[5] Prolonged salicylate ingestion has been reported to induce a mild Cushing's state.[6] It has been proposed that salicylates may exert their influence through the pituitary; through the adrenal cortex, or on the level of circulating steroids, their utilization, or excretion,[7-9] despite some evidence to the contrary.[10-12] Conflicting reports have appeared concerning the effect of salicylates on urinary steroid excretion and on plasma steroid levels.[13-16]

The present investigation was designed to study the acute effects of ASA ingestion in high therapeutic doses on the plasma concentration of corticoids and on the urinary excretion of neutral 17-ketosteroids and corticosteroids.

Methods

Healthy adults and adults with rheumatoid arthritis were studied. In both instances the study program was the same. On the first day, blood was drawn in the fasting state at 8:00 a. m., noon, and 4:00 p. m. to measure the diurnal variation of plasma corticoids. No medications were allowed within the preceding 48 hours. Blood was drawn in heparinized syringes and centrifuged immediately. On all following days similar sampling procedure was followed, but on the second day 30 units of corticotropin (ACTH, Armour) was administered intravenously in 500 cc. of 5% dextrose in water over the six-hour period from 9:00 a. m. to 3:00 p. m.

A period of at least one week was allowed before the same schedule was repeated; but on Days 3 and 4, ASA, 30 mg. per kilogram of body weight, was given at 8:05 a. m., 10:00 a. m., and noon. Each patient was used as his own control. The response to ASA was measured by its effect on the diurnal variation of plasma free reducing steroids and on the response of plasma steroid concentration to corticotropin infusion.

The extraction, the chromatography, and the estimation of total reducing and 17-hydroxycorticosteroids have been described elsewhere, with use of the tetrazolium and phenylhydrazine reactions, respectively.[17,18] The former were designated tetrazolium blue-reducing steroids (TBRS), the latter, phenylhydrazine-reacting steroids (PRS). The difference between these two values is designated the tetrazolium blue fraction. Tetrazolium blue will react with all steroids with a reducing side-chain attached to the 17 position.[19] This will include all adrenal steroids except those in which the keto group of the side-chain has been reduced, including Compounds A (dehydrocorticosterone), B (corticosterone), E (cortisone), F (hydrocortisone), Q (desoxycorticosterone), and S (11-desoxy-17-hydroxycorticosterone), as well as desoxycorticosterone acetate (Doca) and aldosterone. The phenylhydrazine reaction requires, in addition to the reducing side-chain mentioned above, a hydroxyl group on the 17 position; corticoids possessing this configuration include Compounds E, F, and S. Plasma salicylate levels were determined by the method of Chiang and Freeman.[20] Urinary creatinine was measured by the alkaline picrate method[21]; urinary neutral 17-ketosteroids, by the Zimmerman reaction,[22] and corticosteroids, by the tetrazolium procedure previously described,[23]

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TABLE 1.—*Diurnal Variation in the Concentration of Free Plasma-Reducing Corticoids*

Category	Samples, No.	Time	Tetrazolium Blue-Reducing Steroids μg./100 Cc.	Phenylhydrazine-Reacting Steroids, μg./100 Cc.	Tetrazolium Fraction, μg./100 Cc.	Phenylhydrazine Reacting of Tetrazolium Blue-Reducing Steroids, %
Normal adult	37	8:00	33.90±5.75	22.73±2.35	11.26±1.66	67
	16	12:00	32.56±5.66	21.74±2.23	10.82±1.58	67
		4:00	32.97±5.70	22.08±2.32	10.89±1.62	68
Rheumatoid arthritic	26	8:00	23.58±5.87	11.63±2.94	11.95±4.76	49
	11	12:00	21.76±5.21	11.51±3.31	10.25±4.14	53
		4:00	21.62±5.73	11.44±3.01	10.18±4.48	53

both as free corticosteroids and following enzymatic hydrolysis with glucuronidase.

Experimental Results

These data were separated into normal and arthritic subjects for the purpose of analysis. The diurnal variation in each group is shown in Table 1. As each patient is used as his own control, the error of differences in fasting blood corticoid levels is minimized. This level varies little in the same person from day to day, as is shown in succeeding tables by the values with their standard deviations of the 8:00 a. m. fasting samples of each person compared to himself.

The influence of ASA on the diurnal variation in the normal adult is shown in Table 2. The mean 8:00 a. m. fasting level of TBRS is 33.99μg/100 cc., with the PRS comprising 67% of the total. With the ingestion of ASA the total level falls 15.48±5.75μg/100 cc. or 45.5% over the subject's control values, mainly at the expense of the PRS fraction. This drop is less pronounced by 4:00 p. m., but after 48 hours of ASA, TBRS has not returned to the control value. Maximal effect was always seen in four hours (noon sample), with some return toward normal by 4:00 p. m.

Similar data were obtained on the arthritic subjects. However, the mean 8:00 a. m. values were significantly lower than in the normal subjects, with the difference largely due to a lower concentration of the PRS; this fraction averaged only 49% of the total reducing steroids. The influence of ASA in the arthritic is qualitatively similar to the normal, but quantitatively less. If, however, this is expressed as per cent decrease (43.7%) in reducing steroids, the result is similar to that obtained on the healthy subjects. Maximal effect was observed in the noon sample, with some increase by 4:00 p. m., as with the control subjects; most of the decrease was at the expense of the PRS. The graphs in Chart 1 show the plasma values for normal and arthritic subjects.

TABLE 2.—*Influence of Ingested ASA on Diurnal Variation in Concentration of Plasma Corticoids in Normal Subjects and in Patients with Rheumatoid Arthritis* *

Category	Sample	No.	Time	Tetrazolium Blue-Reducing Steroids,† μg./100 Cc.	Phenylhydrazine-Reacting Steroids,† μg./100 Cc.	Phenylhydrazine Reacting of Tetrazolium Blue-Reducing Steroids, %	Mean Salicylate Level, Mg./100 Cc.
Normal subjects	Absolute fast., mean	37	8:00	33.90	22.73	67	0
	Control		8:00	− 0.3 ±1.25	+ 0.10±1.24	66	0
	ASA	14	12:00	−15.48±5.75	−12.33±3.43	55	19.48
			4:00	− 7.00±5.37	− 5.80±3.86	62	28.68
		8	48 hr.	− 6.24±3.49	− 4.72±1.60	65	33.38
Rheumatoid arthritis patients	Absolute fast., mean	26	8:00	23.58	11.63	49	0
	Control		8:00	− 0.3 ±1.18	− 0.20±0.84	48	0
	ASA	10	12:00	−10.30±5.01	− 6.66±2.80	30	20.17
			4:00	− 3.92±5.58	− 3.82±2.54	37	29.73

* Each subject was used as his own control.
† Relative change in μg./100 cc. compared with subject as his own control.

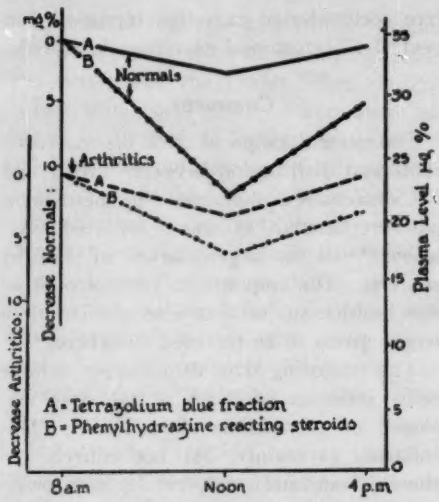

Chart 1.—The influence of ingested ASA on the diurnal variation concentration of free plasma reducing corticoids in normal subjects and in patients with rheumatoid arthritis. The change is expressed in micrograms per 100 cc., in comparison with control values for the same subject.

tropin was an increase of TBRS to 228% of the fasting level, with the per cent of PRS increasing from 67% to 70% of the total. The response to corticotropin in arthritic subjects was somewhat less, 195%; the per cent PRS rose from 43% to 46%.

The effect of ASA on the response to corticotropin in the normal adults is shown in Table 4. Each patient serving as his own control, his responses with and without ASA were compared, as was done with the preceding data on diurnal variation. The ASA effect is mainly on the PRS, resulting in a decrease in the response to corticotropin as judged by the plasma concentration of steroids.

Similar data for the arthritic subjects (Table 4) demonstrate an effect qualitatively similar to the normal and quantitatively similar if considered in the light of lower initial fasting values. Chart 2 shows

TABLE 3.—*Corticotropin Response of Healthy and Arthritic Subjects as Determined by the Concentration of Free Plasma Reducing Corticoids* *

Category	Subjects, No.	Time	Tetrazolium Blue-Reducing Steroids, μg./100 Cc.	Phenylhydrazine-Reacting Steroids, μg./100 Cc.	Phenylhydrazine Reacting of Tetrazolium Blue-Reducing Steroids, %
Normal subjects	8	8:00	34.68± 3.08	23.27± 3.17	67
		12:00	53.33±11.58	37.14± 8.46	70
		3:00	79.40±17.56	55.74±13.45	70
Rheumatoid arthritis patients	6	8:00	24.28±10.40	10.55± 4.74	43
		3:00	44.45±14.05	20.47± 4.04	46

* 30 units of corticotropin in 5% dextrose in water infused intravenously from 9:00 to 3:00 a. m.

Plasma corticoid concentrations before and after corticotropin infusion are shown in Table 3. The normal response to corticotropin graphically the influence on the response to corticotropin of ingested ASA of both the normals and the arthritic subjects.

TABLE 4.—*Influence of Ingested ASA on Response to Corticotropin, as Determined by the Concentration of Plasma Corticoids in Normal Subjects and Patients with Rheumatoid Arthritis* *

Category	Sample	No.	Time	Tetrazolium Blue-Reducing Steroids,† μg./100 Cc.	Phenylhydrazine-Reacting Steroids,† μg./100 Cc.	Phenylhydrazine Reacting of Tetrazolium Blue-Reducing Steroids, %	Mean Salicylate Level, Mg./100 Cc.
Normal subjects	Absolute fast., mean	37	8:00	33.99	22.73	67	0
	Control		8:00	— 1.73±2.12	— 1.34±1.88	68	0
	ASA & corticotropin	7	12:00	— 7.28±4.82	— 5.58±3.00	63	19.92
			3:00	—17.17±6.65	—13.43±4.84	63	23.13
Rheumatoid arthritis patients	Absolute fast., mean	26	8:00	23.58	11.63	49	0
	Control	5	8:00	+ 0.00±4.74	— 0.80±2.19	48	0
	ASA & corticotropin		3:00	—13.2 ±7.32	— 7.50±2.95	49	29.17

* Each subject was used as his own control.
† Relative change in μg./100 cc., compared with subject as his own control.

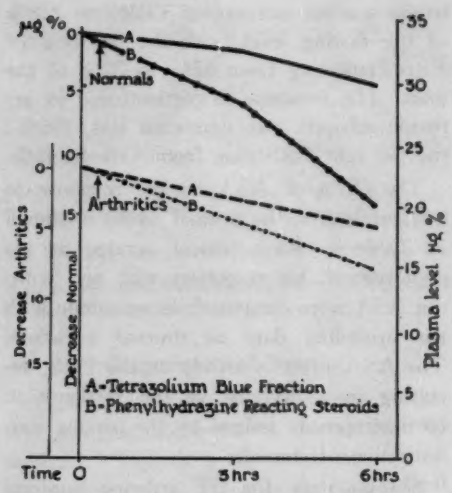

Chart 2.—The influence of ingested ASA on the response to corticotropin as determined by the concentration of plasma corticoids in normal subjects and patients with rheumatoid arthritis. The change is expressed in micrograms per 100 cc., in comparison with control values for the same subject.

free corticosteroid excretion increased, but neutral 17-ketosteroid excretion decreased.

Comment

The normal range of free plasma corticoids and distribution between TBRS and PRS fractions as determined by these methods are similar to those reported elsewhere[18] on a larger series of healthy subjects. The response to corticotropin of the healthy subjects is also similar to a larger group to be reported elsewhere.[24]

The preceding data demonstrate definite acute influence of ASA at the dose employed on the plasma steroid level. This influence is mainly, but not entirely, on the PRS and uniformly results in a lowering of plasma levels most marked in the 4-hour samples but persisting for as long as 48 hours. The effect in the normal person is qualitatively the same as in the arthritic but quantitatively greater. ASA reduced the plasma corticoid response to corticotropin infusion. The limitations in specificity of both reactions make it impossible to state just which compound may have been most affected by salicylate administration. However, it was probably hydrocortisone (Compound F), since this

TABLE 5.—*The Influence of ASA on Urinary Steroid Excretion in Normal Subjects*

	Control Value	Change over Control		
		No Medication	ASA, 90 Mg./Kilogram/Day	
			24 Hr.	48 Hr.
Neutral 17-ketosteroids, mg./24 hr.	10.47±3.19	−0.55±0.67	+3.10±1.60	+3.67±1.88
Free tetrazolium blue-reducing steroid, mg./24 hr.*	1.29±0.15	+0.02±0.06	+0.50±0.17	+0.73±0.28
Glucuronidase-hydrolized tetrazolium blue-reducing steroids, mg./24 hr.*	11.41±1.82	+2.59±1.20	+8.10±1.30	+5.62±2.83
Glucuronidase-hydrolized phenylhydrazine-reacting steroids, mg./24 hr. *	12.10±1.61	0.40±0.30	+8.00±1.52	+4.70±3.87

* Desoxycorticosterone acetate (Doca), standard.

Urine for analysis was obtained from normal persons during two control 24-hour periods, during the ingestion of ASA and during the infusion of corticotropin (6 hours), with and without ASA ingestion. Table 5 shows the effect of ASA ingestion compared to control values on urinary steroid excretion. ASA results in an increase in neutral 17-ketosteroids and in both free and conjugated corticosteroids, persisting for 48 hours. In Table 6 the urinary steroid excretion during corticotropin infusion is tabulated. Corticotropin results in high excretion values for both neutral 17-ketosteroids and free corticosteroids for the six-hour period. With ASA ingestion during the period of corticotropin infusion,

TABLE 6.—*The Influence of ASA on Urinary Steroid Excretion During Corticotropin Infusion in Five Normal Subjects*

Category	Neutral 17-Ketosteroids, Mg./6 Hr.	Free Corticosteroid, Mg./6 Hr.
During corticotropin infusion	8.55±1.37	1.09±0.28
During corticotropin infusion and ASA ingestion	3.84±1.06	1.74±0.66

compound is regarded as normally making up the largest fraction of plasma corticoids that reacts with the Porter-Silber reagent.

The urine data show a consistent increase in neutral 17-ketosteroid excretion and both free and conjugated corticosteroid excretion with ASA ingestion. ASA has been reported to augment urinary steroid excretion over longer periods than studied here.[15] Urinary excretion during the six-hour period of corticotropin infusion with ASA compared to that with corticotropin alone shows a consistent increase in the excretion of free reducing steroids. Conversely, in the same specimens, the neutral 17-ketosteroid excretion during corticotropin infusion is less with ASA than with corticotropin alone. An acute reduction in ketosteroid excretion has been shown by Gardner, Criegler, and Migeon[25] to occur with probenecid (Benemid) ingestion.

The mechanism of the effect of ASA is not clear from these data. From the urine data one concludes that ASA increases the excretion of reducing steroids, but whether this alone explains the drop in the phenylhydrazine-reacting steroids in plasma or whether peripheral utilization or adrenal function is likewise altered is problematic. Unpublished data indicate that at least part of the effect of ASA on the plasma concentration is secondary to its action on renal economy of the unconjugated circulating corticoids.*

The results obtained in the present study agree with those obtained by Done, Ely, and Kelley[14,16] as regards the acute four-hour effect of salicylates on plasma corticoid concentration but differ as regards the effect of ASA on urinary steroid excretion. The present results also differ in that elevation of plasma corticoid values by high concentrations of salicylates was never observed in either normal or rheumatoid subjects. An increase in plasma corticoids and in the urinary excretion of reducing steroids in salicylate-treated rheumatic fever patients was reported by van Cauwenberge and collaborators.[13,15] No consistent change in 17-ketosteroid excretion was obtained by these investigators. Bayliss and Steinbeck[26] found no effect of acute and chronic salicylate ingestion on the plasma corticoid values of a small group of patients.

The varying findings reported by different investigators may be due to differences in methodology, dosage, or experimental design. That there may also be a species difference in response to salicylates is suggested by the acute increase in plasma corticoids reported to occur in guinea pigs injected with salicylates,[27] whereas unpublished data on the dog indicate that decreased plasma corticoid concentration results from salicylate infusion. That the body rapidy adjusts its endocrine and excretory mechanisms to the effects of ASA is evident from the return toward normal values of the plasma corticoids eight hours after the beginning of salicylate ingestion despite the persistence of a high plasma concentration of salicylates.

The rapid return of plasma corticoid values to normal despite augmented excretion would require increased pituitary function secondary to reduction of the hydrocortisone concentration in the circulation. Whether this balance can be more than temporarily altered cannot be deduced from the present study. Evidence that salicylates may influence adrenal activity via the pituitary has been presented by van Cauwenberge[28] and others.[27] Reports that a Cushing-like state may occasionally be associated with prolonged salicylate therapy[6] would argue for a continuous increase in pituitary function in some instances.

If the effectiveness of salicylate therapy does depend to any degree upon pituitary stimulation and if this stimulation depends on a reduced concentration of plasma corticoids, then it would follow that the effectiveness of salicylate stimulation of the pituitary would be reduced by the simul-

*Preliminary experiments on dogs conducted by two of us (S. F. and J. X. W.) indicate that adult intact dogs respond to ASA infusion by a sharp decline in plasma concentration of corticoids. This decline is prevented by bilateral urethral ligation.

taneous administration of cortisone. If salicylates promote cortisone excretion as these experiments suggest, then the duration of the effects produced by cortisone may be reduced by the concurrent use of salicylates.

Summary

The diurnal variation and response to corticotropin (ACTH) of free plasma reducing steroids in patients with rheumatoid arthritis was similar to that of healthy persons.

Acetylsalicylic acid (ASA) produced an acute decrease of approximately 40% in the total level of plasma corticoids, mainly at the expense of the phenylhydrazine-reacting steroids. This influence was most marked four hours after the initial dose of ASA. Some reduction in plasma corticoid levels persisted during 48 hours of ASA administration to healthy subjects.

An intravenous infusion of 30 units of corticotropin in 500 cc. of 5% dextrose in water resulted in a mean increase in free plasma reducing steroids to 228% of the initial value in the normal adult and to 195% in the group of rheumatoid arthritics. The plasma corticoid response to corticotropin was diminished by the ingestion of ASA in both the normal patients and those with rheumatoid arthritis.

ASA increased the urinary excretion of free reducing corticosteroids during six hours of corticotropin infusion and decreased the excretion of 17-ketosteroids. However, ASA alone over a 48-hour period increased the urinary excretion of neutral 17-ketosteroids and both free and conjugated corticosteroids.

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Fibrinolysis and Changes in Fibrinogen in Multiple Myeloma

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Fibrinolysis has been described in a variety of disturbances. An excellent historical review and discussion of fibrinolysis was published in 1948, by Macfarlane and Biggs.[1] A complete analytical review of fibrinolysis by Astrup appeared in 1956.[2] Acute fibrinolysis has been observed in severe trauma, shock, hemorrhages, burns, and transfusion reactions and following surgical procedures on the lung, uterus, and pancreas.[3-5] Acute fibrinolysis also has followed premature separation of the placenta and other obstetric accidents. In other cases fibrinolytic activity may be chronic, proceeding slowly, as in the patients described in this paper. Such chronic fibrinolysis has been described in acute leukemia,[6] cirrhosis of the liver,[7] a significant percentage of patients with carcinoma of the prostate,[8-10] and rarely in patients suffering from disseminated cancer of the bladder, stomach, breast, etc.[3,11] True fibrinolysis was observed in one case of multiple myeloma and in one probable case of disseminated lupus erythematosus by Waldenström.[12] He suggested that some instances of fibrinolysis in myeloma blood might be explained by the presence of cryoglobulin.

It is the purpose of this paper to report two patients with multiple myeloma, showing an active chronic fibrinolytic process of variable severity as evidenced by fibrinolytic destruction of their own blood clots in vitro. We also wish to report studies of the plasma electrophoretic patterns of these patients and others demonstrating changes in the fibrinogen peaks.

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Methods and Materials

Method of Electrophoresis.—The Spinco Model R. Paper electrophoresis system was used. A sample of 0.01 ml. plasma was applied with the stripper to Whatman 3 mm. filter paper strips. Barbiturate buffer at pH 8.6, of ionic strength μ=0.075 [13] was employed with a constant current of 5 ma. per 8 strips or 10 ma. per 16 strips applied overnight at room temperature. The dried strips were stained with Bromophenyl blue, made translucent with liquid petrolatum (mineral oil), and scanned on the Spinco Analytrol Scanner. Normal control plasmas give a definite fibrinogen peak (Figs. 2 and 3).

Fibrinogen Determination.—Fibrinogen levels were determined by precipitation with calcium chloride and the protein determined by the biuret method. Normal range: 200 mg. to 600 mg. per 100 ml. of plasma.

Cryoglobulin Determination.—Cryoglobulins were tested for as described by Stefanini and Dameshek.[14] Both a positive and negative control were employed.

Fibrinolysis.—Fibrinolysis was determined by the amount of lysis of the whole blood clot during the observed time at 37 C. Normal blood clots show no fibrinolysis in 72 hours at this temperature.

Bleeding Times.—Bleeding times were determined by Duke's method.

Coagulation Times.—Coagulation times were determined by the Lee and White method.

Prothrombin Times.—Prothrombin times were determined by the one stage method of Quick.

Anticoagulants.—Those used were saturated potassium oxalate (1 drop to each 5 ml. of blood) or a mixture of 4 mg. of potassium oxalate with 6 mg. of ammonium oxalate to each 5 ml. of blood.

Report of Cases

CASE 1.—A Negro man, age 64, was admitted to the VA Hospital on Dec. 27, 1955, because of recurrent severe nosebleeds for eight months. The most recent nosebleed had occurred five days before admission and had lasted for one and one-half hours. He had been in this hospital in 1946 for treatment of an abscess. His hemoglobin at that

time was 15 gm., and his sedimentation rate was 2 mm. He was again admitted in 1951, with arthritis and hypertensive cardiovascular disease. His hemoglobin then was 12.5 gm., and his sedimentation rate, 40 mm. There was also a trace of albumin in his urine on that admission.

On this admission the examination of the ears, nose, and throat was negative. Blood pressure was 180/80. Urinalysis showed a trace af albumin and negative Bence Jones reaction. Hemoglobin was 9.1 gm. per 100 cc.; RBC, 2,820,000; WBC, 7600, with platelets 150,000; bleeding time, 1 minute 10 seconds; coagulation time, 10 minutes 10 seconds; prothrombin time, 52% normal; sedimentation rate, 10 mm.; total protein, 13.6 mg. per 100 cc., with albumin 3.3 gm. and globulin 10.3; cryoglobulin, negative; calcium, 5.3 mEq. per liter. X-rays of skull and skeleton were negative. Sternal marrow done Jan. 9, 1956, showed an increase in plasma cells consistent with a diagnosis of plasma-cell myeloma. Despite the transfusion of 3500 cc. of blood, the hemoglobin was 8.3 gm. on discharge on March 22, 1956. He was admitted on April 13, 1956, with a hemoglobin value of 6.0 gm.; RBC, 2,100,000, and WBC, 6500. Proteins were still found to be elevated, varying from 12.0 to 15.6 gm. (total). The highest globulin value reported was 13.4 gm.

A plasma electrophoretic study done on Jan. 30, 1956, showed the absence of a fibrinogen peak, and on Feb. 9, 1956, complete fibrinolysis of the patient's clot was noted in 22 hours at 37 C. Throughout the patient's hospital stay he showed intermittent and variable fibrinolytic activity. See Table 1 and Figures 1 and 2.

TABLE 1.—*Results of Tests for Fibrinolysis and Plasma Electrophoresis*

Case	Date	Clot Lysis at 37C	Typical Fibrinogen Peak Present on Electrophoretic Pattern	Fibrinogen, Mg./100 Cc.
1	1/30/56	----------	Not present	
	2/9/56	4+ 22 hr.	Not present	387
	2/29/56	4+ 2 hr. 15 min.	Not present	337
	3/6/56	4+ 22 hr.	Not present	
	3/15/56	None	Present	
	3/21/56	3+ 12 hr.	Reduced	
	3/22/56	1+ 48 hr.	Reduced	
	6/19/56	4+ 24 hr.	Not present	
		4+ 17 hr.		
	8/30/56	3+ 6 hr.	Not present	
	9/18/56	4+ 8 hr.	Not present	
	10/16/56	None	Present	
	10/22/56	4+ 22 hr.	Not present	
	10/29/56	4+ 22 hr.	Not present	
	10/30/56	4+ 6 ½ hr.	Not present	
	10/31/56	4+ 8 hr.	Not present	
	11/5/56	None	Present	
	11/6/56	None	Present	
2	Mar., 1955	----------	Present	
	2/9/56	4+ 4 hr.	Not present	519
	2/29/56	None	Present	463
	3/6/56	None	Present	
	3/15/56	None	Present	
	3/21/56	4+ 26 hr.	Reduced	
		2+ 26 hr.	Reduced	

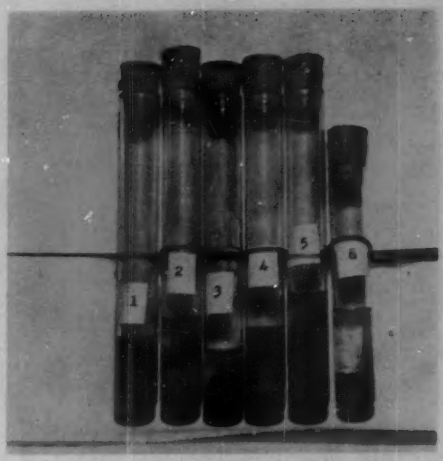

Fig. 1.—Lysis of whole blood clots from Case 1. Tube 1, no lysis of refrigerated clot. Tube 2, clot contracted, RBC settling out of top of clot. Clot incubated 2 hours at 37 C. Tube 3, RBC settling to bottom of clot. Tube 4, RBC settled to bottom of tube, fibrin sac remained in top of tube. Tube 5, fibrin sac has many small clear areas. Tube 6, few fibrin strands remain. No clot or fragments remain when examined on flat surface.

On Sept. 17, 1956, his blood clots lysed completely in 4 hours at 37 C and the electrophoretic pattern of the plasma showed no peak for fibrinogen; on Sept. 18, 1956, the bleeding time was 8 minutes 25 seconds; coagulation time, 15 minutes, and prothrombin time, 59% of normal. At this time superficial hematomas were present. Just prior to death, on Nov. 6, 1956, there was no fibrinolytic activity.

The patient died with generalized bleeding on Nov. 6, 1956, and the autopsy demonstrated massive marrow replacement involving not only the red marrow but to less extent the yellow marrow. Organ infiltration by the myeloma cells was minimal aside from the hilar and mediastinal nodes, where the characteristic architecture was effaced. Multiple small cerebral hemorrhages were found along with moderate bleeding into the subarachnoid space and massive bleeding into the lungs and gastrointestinal tract.

CASE 2.—A white man, age 67, was admitted to VA Hospital on Feb. 14, 1955, with a pathological fracture of the left femur. He had been using crutches since March, 1954, when he had suffered a fracture of the right thigh. He had had several previous admissions to the hospital which show definite relationship to the present admission. In 1948 he was found to have a hemoglobin value of 12.5 gm. and a 2+ albuminuria. In 1950 he was investigated for multiple myeloma because of the x-ray finding of multiple areas of rare-

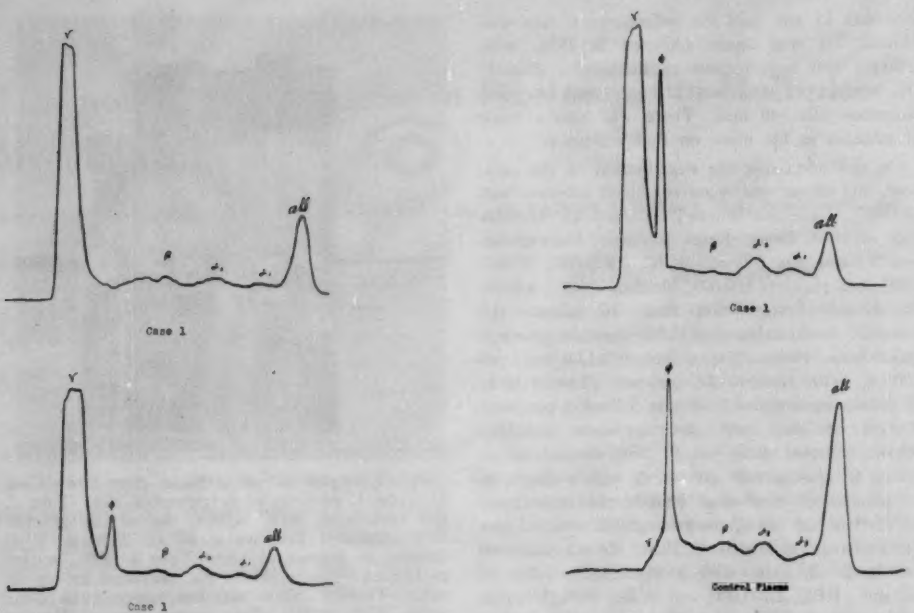

Fig. 2.—Electrophoretic patterns on plasmas from Case 1 and a normal control.

faction in the skull, trace to 4+ albuminuria, a trace of Bence Jones protein on one examination, and an anemia varying from a hemoglobin value of 11 gm. to one of 9.5 gm. The bone marrow examinations were unsatisfactory. An x-ray of the chest showed minimal infiltration in the right upper lobe.

On the present admission x-ray showed diffuse osteolytic lesions throughout the skeleton. At that time he had a fracture of the left femur, and later during his hospitalization he developed fractures of the right tibia and right femur. He showed a 3+ albuminuria, with a positive Bence Jones reaction. The hemoglobin was 7.8 gm.; RBC, 3,100,000, and WBC, 5150. Occasionally plasma cells and nucleated RBC's were seen on the peripheral blood smears. The total protein was 9.9 gm.; albumin, 4.6 gm., and globulin, 5.3 gm. Cryoglobulins were not found. The N. P. N. was 52 mg. per 100 cc., and calcium, 5.4 mEq. per liter. A sternal marrow examination done on Feb. 23, 1955, showed 45% atypical plasma cells. The patient received urethan and deep x-ray therapy throughout most of his hospitalization. Despite numerous blood transfusions the highest hemoglobin determination was 9 gm.

It was first noted on Feb. 9, 1957, that there was complete fibrinolysis of the patient's clot in 4 hours' time at 37 C. A plasma electrophoretic pattern on that date showed no fibrinogen peak (Table 1 and Fig. 3).

The patient became febrile in March, 1956, and died March 26, 1956. At postmortem examination, in addition to evidences of multiple myeloma, he was found to have active bilateral pulmonary TBC, TBC pneumonitis, pleuritis, and enteritis.

Results and Interpretations

Table 1 presents the data on fibrinolysis and fibrinogen serially for the two patients. Figure 1 shows the phenomenon of fibrinolysis in the clots of Case 1. In all examinations the blood of the patients was found to clot normally, and the plasma was always found to be clottable with thrombin if this test was done soon after the blood was drawn. These observations indicate that fibrinogen was present when the blood was drawn but that the clot which was formed was not stable under usual laboratory conditions.

Figures 2 and 3 present the different plasma electrophoretic patterns on the patients as compared to a control plasma studied under the same conditions. These patients demonstrated changes in their fibrinogen peaks which correlated with the

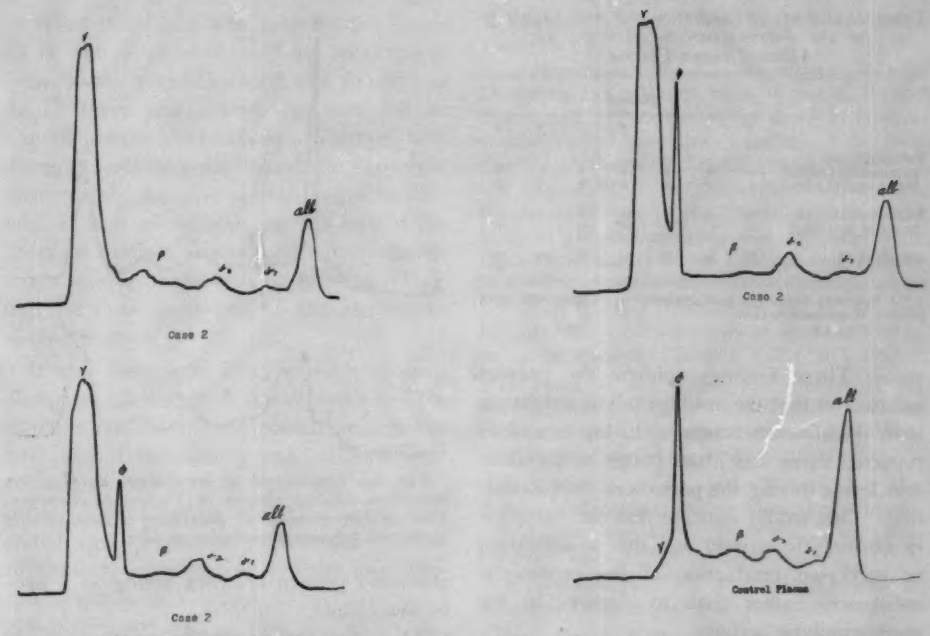

Fig. 3.—Electrophoretic patterns on plasmas from Case 2 and a normal control.

in vitro fibrinolysis. When the fibrinolytic process was active the fibrinogen peak disappeared from the spectrum, whereas this peak was observed when such activity was absent. Even when the fibrinogen peak was absent the plasma was clottable with thrombin and the quantitative fibrinogen level was normal. It is possible that destruction of the fibrinogen occurred during the process of electrophoresis producing the altered pattern.

Additional studies were done on the plasma of Case 1 at a time (Aug. 29, 1956) when fibrinolysis was very active, with complete destruction of the blood clot in 6 hours at 37 C. This plasma was found to be clottable with thrombin immediately after being drawn. If it was allowed to incubate at 37 C overnight it was no longer clottable. This change did not occur in this length of time if the plasma remained at room temperature. If incubation was carried out for only 6 hours, the plasma was still clottable. This suggests that the proteolytic enzyme is active on both fibrin and fibrinogen but more active on fibrin, the activity depending on conditions primarily of temperature. This difference in the activity of proteolytic enzymes has been demonstrated and suggested by other investigators.[3,13,14]

Three other patients with multiple myeloma were observed on one or more occasions, at which times they did not demonstrate either active fibrinolysis or changes in the fibrinogen peaks of their electrophoretic patterns.

Table 2 and Figure 4 present additional studies done on normal and low-albumin (below 50%) plasmas. Normal plasmas always gave a definite fibrinogen peak. In the low-albumin plasmas, a normal fibrinogen peak was present if electrophoretic studies were done immediately, but it was possible to alter this by incubating the plasma at 37 C, which caused the fibrinogen peak to decrease or disappear. This change could be elicited in most low-albumin plasma samples collected with potassium oxalate but seldom in those collected with potassium ammonium oxalate. It would appear that in patients with low-albumin plasmas the fibrinolytic substances can be more easily acti-

TABLE 2.—*Effects of Incubation and Anticoagulants on the Fibrinogenolytic Activity of Low-Albumin Plasma*

	Patient *						
	3	4	5†	6	7	8	9
Potassium and ammonium oxalate	+	+	+	0	0	+	0
frozen at 37C 4 hr.	+	+	+	0	0	0	0
Potassium oxalate	+	+	+	+	+	+	+
frozen at 37C 4 hr.	—	—	—	—	—	—	+
Albumin, %	35	34	35	44	37	48	46

* + indicates fibrinogen peak present; —, no fibrinogen peak present; 0, no pattern run.
† See Figure 4.

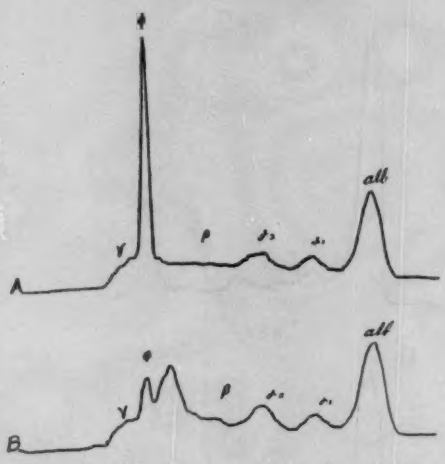

Fig. 4.—The effects of incubation at 37 C on potassium oxalate plasma of Patient 5. *A*, potassium oxalate plasma. *B*, potassium oxalate plasma incubated 4 hours 40 minutes at 37 C.

vated. These findings confirm the present impression that the antifibrinolytic substance is in the albumin fraction. In the two cases reported there was little change in the albumin levels during the periods of hospitalization. This would indicate that the variation in fibrinolytic activity was due to activation or increased production of the proteolytic substances rather than to changes in the antifibrinolytic activity.

Comment

Recently there has been much interest in the bleeding-tendency in diseases which have abnormalities in plasma proteins such as multiple myeloma. Stefanini and Dameshek summarize the causes of such bleeding as follows: (*a*) thrombocytopenia, (*b*) infiltration of the vascular wall by the abnormal protein, and (*c*) abnormalities of the process of blood coagulation involving particularly the conversion of fibrinogen to fibrin.[15] This interference with fibrin formation has been explained by several hypotheses. The excess globulin found in multiple myeloma may bind calcium and perhaps other plasma factors which are necessary for optimal conversion of fibrinogen to fibrin. Craddock et al. have reported a case of multiple myeloma in which there was total gel formation of the blood or plasma without development of fibrin strands.[16] They compared their case to two similar cases reported by Luescher and Labhart[17] and Uehlinger[18] in which the authors concluded that the conversion of fibrinogen was blocked at an intermediary phase ("profibrin") by the abnormal protein complex acting as a protective colloid.

These two patients exhibit another way in which diseases with dysproteinemia can interfere with the coagulation mechanism. It is interesting that one patient, Case 2, had no hemorrhagic phenomena and that the other patient, Case 1, had only mild hemorrhagic symptoms prior to the terminal bleeding episode. Since routine examinations for fibrinolysis are not done, it is possible that many similar cases have been overlooked in the past.

Much of the work which is now being done in the field of fibrinolysis concerns the mechanism of activation of the proteolytic enzyme, plasmin. These two cases cast little light on this mechanism but do demonstrate a variable amount of spontaneous lytic activity which has developed in these patients, apparently due to the malignant process which is present.

Summary

Two cases of multiple myeloma, in which a chronic fibrinolytic process of variable activity was present, are reported. It was felt that this was due to an activation or increased production of proteolytic substances in the blood.

When this fibrinolytic activity was found to be active, as evidenced by spontaneous lysis of the patient's blood clot in vitro at 37 C, there was always demonstrated an altered plasma electrophoretic pattern, with disappearance or reduction of the fibrinogen peak. Since the plasma was found to contain a normal amount of fibrinogen on chemical analysis, it was felt that this change might be due to the lysis of fibrinogen during the time consumed in the process of electrophoresis.

It was possible to bring about this same change in fibrinogen in other plasmas if the albumin content of the plasma was below 50% and if the plasma was collected with potassium oxalate and incubated at 37 C before electrophoresis was done. This suggested that there was a decrease in the antiproteolytic substances of these low-albumin plasmas in contrast to the increased proteolytic activity in the two cases reported.

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Case Reports

Heart Involvement in Infectious Mononucleosis

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Considering the high incidence of infectious mononucleosis, the clinical recognition with pathologic confirmation of myocarditis due to this disease is rare. This complication has been known for many years, having been described by British authors,[1] who noted cardiac dilatation and transient murmurs occurring in cases of "epidemic cervical adenitis." Reports of electrocardiographic changes date back to Longscope,[2] who noted inverted T waves. With more routine use of the electrocardiograph the incidence of transient abnormalities, such as T-wave changes and conduction disturbances, has been found to be quite high, occurring in 41% of one series.[3] In a recent editorial evaluation of the subject, Houck[4] reemphasized the need for cautious interpretation of T-wave changes, stating that they may occur in the presence of fever, drugs, and autonomic nervous system disturbances.

A review of the literature reveals a paucity of pathologic material available for the study of myocardial involvement in infectious mononucleosis. Saphir[5] exhaustively reviewed all types of myocarditis, and infectious mononucleosis is not mentioned as an etiological category. However, in a later survey he and Gore[6] listed infectious mononucleosis in a table of diseases associated with myocarditis without presenting further details. Only one death attributed to infectious mononucleosis myocarditis has been reported,[7] but this occurred in a patient who also had sepsis. Ziegler[8] first reported the autopsy study of the heart in a fatal case of infectious mononucleosis. He found the heart remarkably free of cellular infiltrate, and he described only acute changes common to many infectious diseases. Brien's findings[9] in two cases consisted of small accumulations of mononucleosis cells in the heart muscle and under the endocardium. Allen and Kellner[10] reported a case of a 23-year-old man who was killed in an accident one month after clinical recovery from infectious mononucleosis. There had been no cardiac symptoms during the acute phase, but at autopsy focal collections of monocytes and lymphocytes without replacement of muscle fibers were observed. Autopsy studies of two cases complicated by the Guillain-Barré syndrome revealed absence of myocardial involvement.[11] Custer and Smith[12] reported an unusually large series of eight fatal cases of infectious mononucleosis. In none of these cases was death attributed by them to myocarditis. In six cases perivascular lymphocytic cellular collections in the myocardium and endocardium were found. There was no necrosis of muscle tissue or serosal reaction. In another fatal case with neurologic complications moderate edema of the myocardium and loss of striations in a few fibers were found.[13]

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Report of Case

First Admission (Jan. 11-22, 1957).—The patient was a 20-year-old Ohio State University student. His illness began two days prior to admission, with pleuritic pains in the left axillary region and a hacking nonproductive cough. He had experienced no chills, fever, sore throat, or coryza. Chest x-ray (Fig. 1) at the Student Health Service revealed a small infiltrate in the

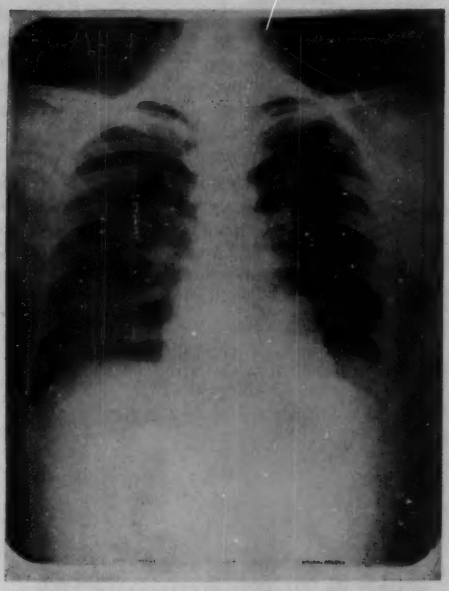


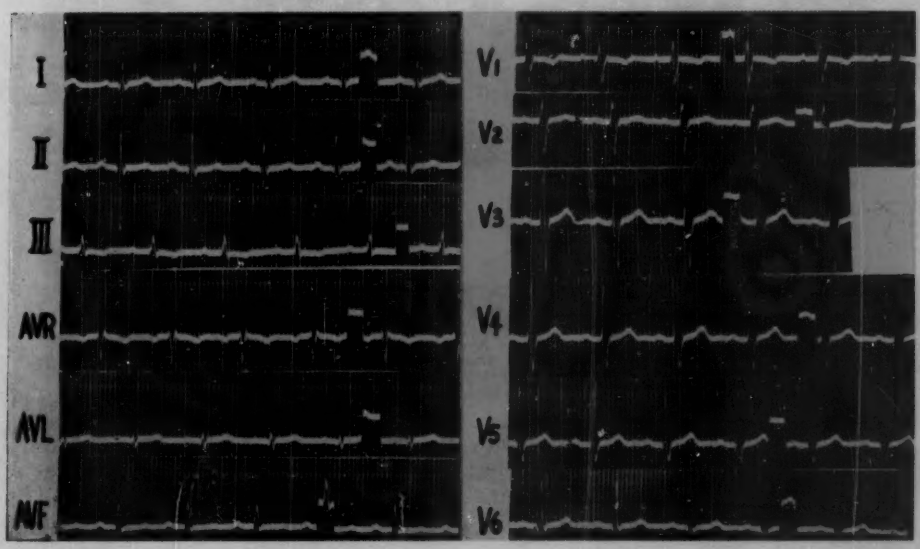
Fig. 1.—Initial chest x-ray, showing small infiltrate in the left base, with a small pleural effusion.

left base and a small pleural effusion, and he was admitted to the Infectious Disease Service. Prior to this illness he had been in perfect health. The family history and system review were not remarkable.

Physical examination on admission disclosed an athletic-appearing white youth in no distress. The height was 6 ft. 1 in., and the body weight, 184 lb. The temperature was 100.4 F orally; pulse, 88 per minute and regular; blood pressure, 120/70; respirations, 24 per minute. The skin was warm and dry. Except for a small nontender node under each angle of the jaw there were no palpable lymph nodes. No significant abnormalities of the eyes, ears, and nose were noted. The pharynx was not inflamed, and the neck was supple, without thyroid enlargement. The left hemithorax was splinted. High-pitched suppressed breath sounds and a pleural friction rub were heard over the left lung base at the angle of the scapula. The breath sounds were normal on the right. The heart was of normal size and the heart tones of good quality. Neither pericardial rub nor cardiac murmur was present. The abdomen was not tender; liver, kidneys, and spleen were not palpable. The nervous system and musculoskeletal system were intact.

Admission laboratory studies showed a white blood cell count of 10,900 with 58% neutrophils, 39% lymphocytes, 2% monocytes, and 1% eosinophils; no abnormal lymphocytes were seen; the red blood cell count was 4,300,000; hemoglobin, 13.5 gm. per 100 cc. VDRL test was negative. Cold agglutinins were 1:16. The admitting diagnosis was primary atypical pneumonia. Therapy consisted of tetracycline, 500 mg. every six hours, and symptomatic medication for cough and chest pain. On Jan. 15, 1957, an electrocardiogram (Fig. 2) disclosed a rate of 100 per minute; sinus rhythm;

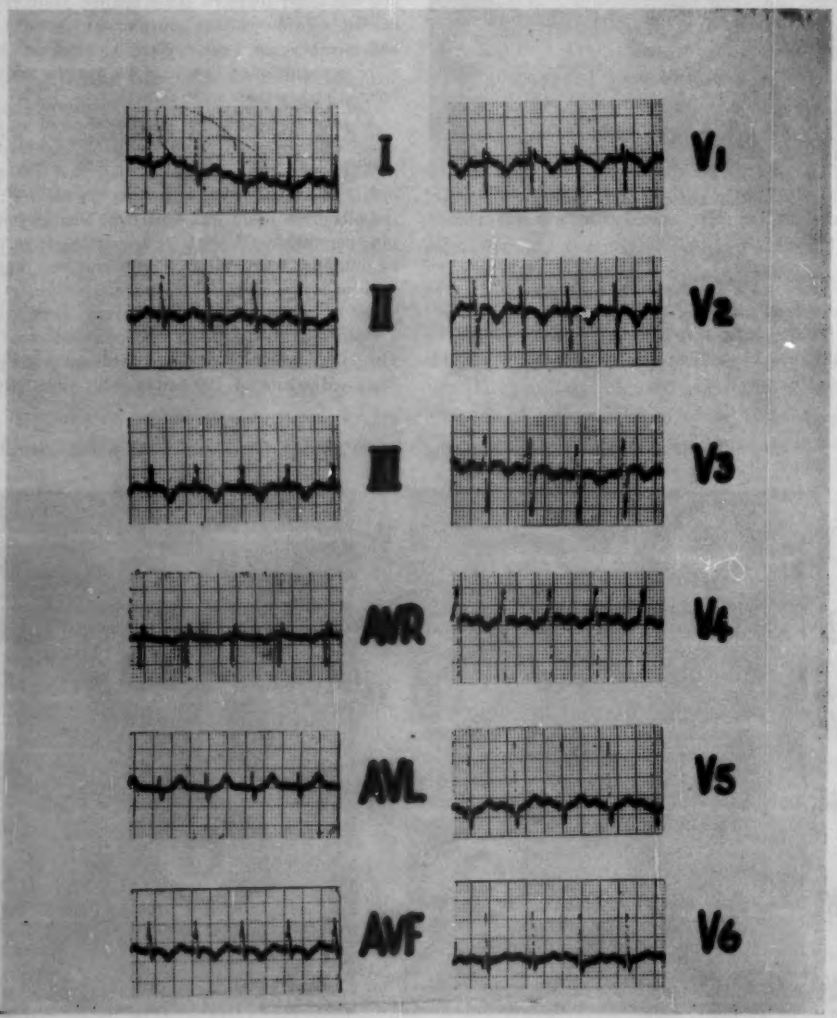
Fig. 2.—Initial electrocardiographic tracing (Jan. 15, 1957), considered to be within normal limits.



P-R interval, 0.18 second; QRS interval, 0.08 second; ST segment, isoelectric, and T wave upright in all leads except Leads III and aV_R. This record was considered to be within normal limits. On Jan. 15, 1957, the heterophil antibody titer was 1:448 after guinea-pig absorption. On Jan. 18 the heterophil titer was 1:896 after guinea-pig absorption. Blood cell counts on this day disclosed a total WBC count of 9800, with 54% neutrophils, 37% lymphocytes, 5% eosinophils, 2% monocytes, and 2% "abnormal" lymphocytes. Cold agglutinations were negative.

The positive heterophil titer was a surprise, and with attention focused on infectious mononucleosis as the etiologic factor careful daily observations were made for the known common manifestations. Throughout this admission he developed no sore throat, rash, or jaundice. Pericardial rubs, murmurs, and abnormal neurologic signs were not observed. Hepatosplenomegaly was never detected, nor was there any increase in the size of accessible lymph nodes. The temperature ranged between 99 and 100.6 F for the first week, and there was slow clearing of the pulmonary signs. On the eighth

Fig. 3.—Second electrocardiogram, taken after the appearance of clinical signs of myocarditis (Jan. 24, 1957). T-wave and S-wave changes are evident when compared with the original base line tracing. In addition there has occurred a mild widening of QRS.



hospital day there was considerable subjective improvement, with some hacking cough persisting. During the last three days in the hospital he was afebrile and essentially symptom-free. The lungs were clear to auscultation and percussion. Chest x-ray on Jan. 21, 1957, showed definite improvement, but blunting of the left costophrenic sinus was still present. He was discharged on Jan. 22, with instructions to return for a follow-up in 24 hours.

Second Admission (Jan. 23-25, 1957).—The following morning he was awakened in his dormitory by severe bilateral pleuritic pain and experienced chills, fever, and dyspnea. There was a marked increase in cough, which was nonproductive. He was readmitted directly to the hospital ward. He was found to be slightly dyspneic at rest but without cyanosis or neck-vein distention. The oral temperature was 101 F; blood pressure, 120/68; pulse, 92; respirations, 30 per minute. The pharynx was clear. One small node was palpable in each axilla. The lungs were clear to percussion and auscultation. No pleural friction rub was detected. The cardiac apical impulse was in the fifth left interspace, 13 cm. from the midsternal line.

Fig. 4.—Electrocardiogram taken terminally, showing complete right bundle-branch block (Jan. 25, 1957).

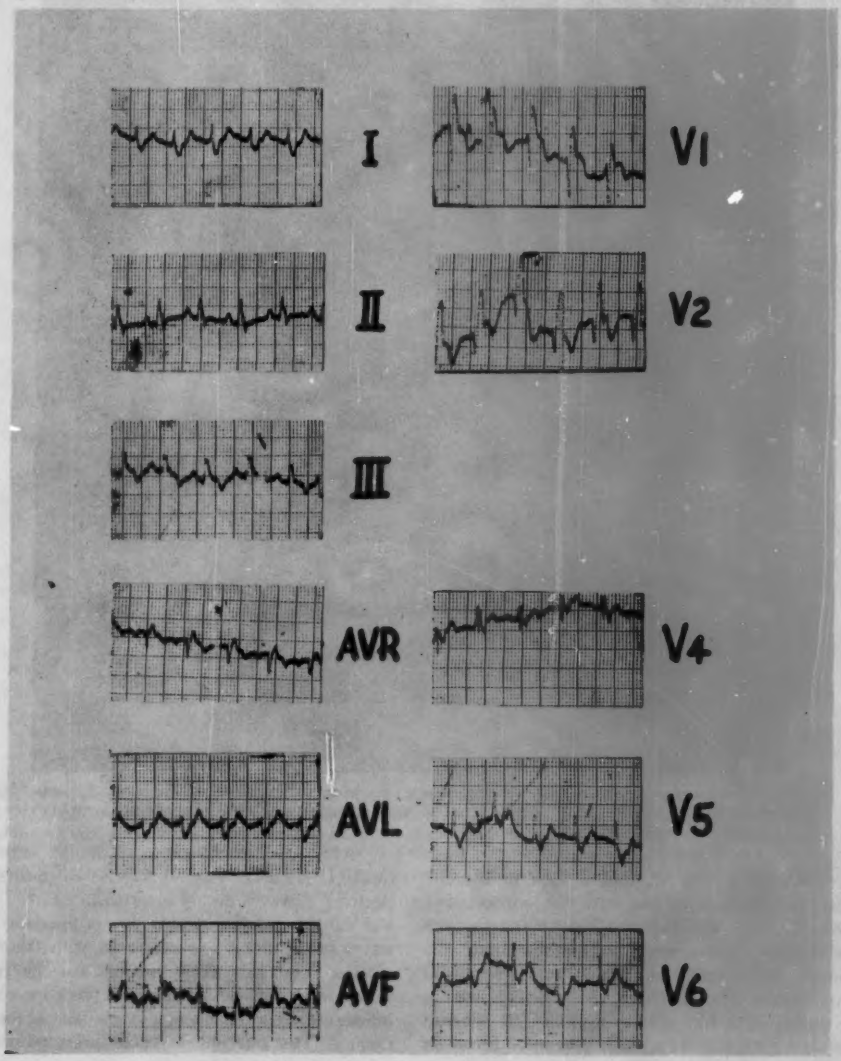


Fig. 5.—Transverse section of myocardium, showing infiltration of interstitial tissue by inflammatory cells, with dense rounded nuclei and scanty cytoplasm resembling lymphocytes; hematoxylin and eosin; × 100.

The apical rate was 92, and a loud midsystolic apical gallop was present. At the xiphosternal junction a transient soft pericardial friction rub was audible. There were no murmurs, and the pulmonic second sound was not accentuated.

An electrocardiogram (Fig. 3) on the following day showed rate, 100; a sinus rhythm; PR interval, 0.16 second; QRS, 0.10 second; deep S waves in Leads I, II, aV_F, V_5, and V_6; ST segments, isoelectric; T waves deeply inverted in Leads II, III, V_1, V_3, V_5, and V_6, and there was lowering of T waves in V_5 and V_6 as compared with the record of Jan. 15, 1957. This tracing was interpreted as showing myocardial changes and increase in intraventricular conduction time since the last tracing. The antecubital venous pressure was 180

Fig. 6.—Detail of a focus of necrosis. Three involved heart-muscle fibers can be seen running slightly obliquely across the field. The middle one shows early changes of necrosis, consisting of loss of architecture with fragmentation of myofibrils. The fibers above and below this one show nearly complete dissolution of the fiber, with infiltration of inflammatory cells into the area. At the top and bottommost portion of the figure normal-appearing muscle fibers can be seen. There were hundreds of these foci of necrosis observed, mostly located in the right ventricle; hematoxylin and eosin; × 620.

mm. of water; circulation time arm-to-tongue was 23 seconds. On admission a chest x-ray was reported as showing the heart size to be within normal limits and the lung fields clear.

Nasal oxygen was started, and within 30 minutes there was marked relief of the dyspnea; he spent a comfortable night. It was felt that this series of events represented acute myocarditis due to infectious monoucleosis.

The following day he was much improved and cheerful. The pericardial rub was gone; the gallop rhythm was barely perceptible. However,

embryocardia persisted. The blood pressure was recorded as 110/70, and the pulse was 90 per minute. The liver edge was palpable at the right costal margin and was nontender. The spleen could not be felt.

Admission laboratory studies showed hemoglobin, 14 gm. per 100 cc.; RBC, 4,950,000; WBC, 5500, with 55% neutrophils, 34% lymphocytes, 3% eosinophils, 3% atypical lymphocytes, and 5% monocytes. The blood urea nitrogen was 19 mg.; total bilirubin, 1.0 mg.; cephalin flocculation, 1+; cold agglutinations, negative; urine, normal. The heterophil titer was 1:896 after guinea-pig absorption. Serum glutamic oxalacetic transaminase was 50 units, 0-30 units being normal.

At 11 p. m. he suddenly became extremely dyspneic, apprehensive, and deeply cyanotic. The pulse rate was 120 per minute, but the blood pressure was unobtainable. Levarterenol (Levophed) infusion was begun. An electrocardiogram (Fig. 4) demonstrated complete right bundle-branch block just prior to death. Resuscitation of the heart beat with cardiac massage was attempted unsuccessfully. The antemortem diagnosis was acute cor pulmonale due to pulmonary embolus secondary to intracardiac thrombosis, which in turn was due to acute myocarditis of infectious mononucleosis. An autopsy was performed two hours after death.

*Partial Autopsy Report**.—The heart weighed 400 gm. The pericardium was not thickened, and the serosal surface was smooth and shiny. The chambers were not dilated and were empty except for a friable reddish brown thrombus 0.75 cm. long, attached to the wall of the right auricular appendage. The mural endocardium was smooth and shiny. The valves showed no deformities or vegetations and were of normal circumference. The myocardium was somewhat soft and flabby. The coronary arteries were thin-walled and widely patent. Microscopically a moderate diffuse infiltration of inflammatory cells was seen in the interstitial tissue, quite often located perivascularly. Some of these cells were large mononuclear ones, with large, moderately vesicular, slightly irregular nuclei containing small to large chromatin clumps. The cytoplasm was moderate in amount and faintly basophilic, without granules. The endothelial cells lining the capillaries were swollen. In other areas these interstitial cells were swollen. In other areas these interstitial cells were smaller, with dense rounded nuclei and scanty cytoplasm resembling lymphocytes (Fig. 5).

The most striking change consisted of numerous focal microscopic areas of necrosis of heart muscle fibers, with partial to complete fragmentation of from two to three fibers in each focus with loss of nuclei. The mononuclear cells infiltrated these areas invariably and seemed to be invading the muscle fibers, some of which were broken down almost completely (Fig. 6). The fibers surrounding these focal areas of necrosis showed no change. These changes were markedly more pronounced in the right ventricle than in the remaining portions of the heart.

The epicardium showed a mild chronic inflammatory reaction. A few scattered areas of petechial hemorrhage were seen in various areas under the epicardium, which we attributed to the terminal cardiac massage.

The right lung weighed 370 gm. and showed the usual gross and microscopic picture except for mild atelectasis. The left lung weighed 300 gm. and was completely atelectatic. This change was attributed to pneumothorax secondary to the terminal thoracotomy for cardiac massage. The pleura showed no reaction in any area. A 4 cm. reddish-brown, friable, rather firm embolus with a very slightly coiled contour was found in the left main pulmonary artery not attached to the wall. It appeared about two to three days old, with beginning organization seen histologically. Microscopically the left lung tissue showed only atelectasis.

The spleen was enlarged and weighed 400 gm., with a prominent follicular pattern seen on cut section. Microscopically the spleen was congested. There were present numerous cells containing dark-brown pigment granules taken to be hemosiderin. A mild infiltration of lymphocytic cells was seen in the trabeculae and perivascular adventitia. Numerous eosinophils and an occasional normoblast were seen in the red pulp.

The liver was enlarged and weighed 2400 gm. Microscopically numerous small focal areas of liver-cell necrosis were observed, with infiltration of small cells having markedly lobulated nuclei occurring in these areas. Occasional eosinophilic granulocytes were seen in the sinusoidal lumen.

In general the lymph nodes were only slightly enlarged in the axillary, hilar, and abdominal regions. The abdominal and axillary nodes showed rather atrophic lymphoid follicles, with reticulum-cell hyperplasia. In addition a fair number of large cells with abundant, faintly basophilic vacuolated cytoplasm and rather large indented to bilobed nuclei were seen in the interstices. These corresponded to the most characteristic cell type described by Downey[14,15] in infectious mononucleosis.

The remainder of the organs showed no important changes. No peripheral source for the pulmonary embolus was found. The brain was not examined.

* The interpretations herein presented were reviewed by Dr. Emmerich von Haam, Chairman, Department of Pathology.

Comment

Although the hematologic picture was not particularly characteristic and the peripheral lymph nodes were not strikingly enlarged, the diagnosis of infectious mononucleosis could be made beyond doubt. The initially high and rising heterophil titer and the pathologic findings are sufficient criteria. The heterophil titer was obtained early in the course of the illness primarily because of the high index of suspicion in treating university students rather than to confirm an initial clinical impression. It would therefore seem advisable to obtain a heterophil titer on all obscure or atypical cardiorespiratory disease cases, especially in young adults.

The cardiac findings at autopsy were exceedingly interesting because of the unusual opportunity to correlate these with the clinical events. The appearance of gallop rhythm aroused strong suspicion of acute myocardial involvement. The electrocardiographic changes and elevated venous pressure furnished additional evidence. The clinical and electrocardiographic changes in myocarditis were recently reviewed by de la Chapelle and Kossmann,[16] who stated that the usual lesions in myocarditis are focal and the QRS changes are minimal. The modification of the QRS complexes in the case presented here indicated an intraventricular block, which is consistent with extensive myocardial involvement. The microscopic foci of necrosis and inflammation seen here were so widespread as to constitute a diffuse process.

Of further interest is the fact that the right precordial leads V_1, V_2, and V_3 showed deep T-wave inversion, and the T waves in the left precordial leads V_4, V_5, and V_6 were consistently upright. It is possible that this correlates with the more extensive involvement seen histopathologically in the right ventricle. The occurrence of complete right bundle-branch block which was observed here is a well-known electrocardiographic finding in acute right-heart strain due to pulmonary embolism. Although the autopsy findings indicate that the embolism occurred approximately two days before death, the classical clinical and electrocardiographic manifestations were terminal events. Although the complete right bundle-branch block could conceivably have been caused by foci of necrosis in the main right bundle of His, it seems more probably the result of acute right heart strain.

De la Chapelle and Kossmann are of the opinion that intracardiac thrombosis as we observed here is not uncommon in myocarditis, especially in the Fiedler type, and that emboli may be a cause of sudden death even when there is no evidence of infection.

Fortunately this complication of infectious mononucleosis is rare considering the incidence of the disease. In light of this case, however, the widespread concept[4,17] that there is little to fear from infectious mononucleosis and its heart complications should be revised. Our findings here demonstrate that the etiological agent (or agents) causing infectious mononucleosis is capable of causing necrosis of the heart muscle fibers as well as the previously reported infiltration of the myocardium by inflammatory cells.

Summary

An unusual fatal case of infectious mononucleosis with acute myocarditis is presented.

Death occurred from massive pulmonary embolism arising from the heart.

The degree of myocardial involvement seen here has not been previously reported in infectious mononucleosis.

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Solitary Benign Adenoma of the Liver Associated with Progressive Hepatic Insufficiency

Report of a Case with Autopsy Findings

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Benign adenomas of the liver are observed infrequently. An unusual opportunity was provided to study the effects of such a tumor in a girl who was followed for several years because of recurrent and progressive signs of hepatic insufficiency. Ultimately, abdominal exploration disclosed a large solitary tumor of the liver. Histologically, this consisted of masses of liver cord cells. After attempted extirpation of the tumor, the patient died and was autopsied. Both gross and histologic studies lent support to the concept that this tumor was benign. Of special interest was the fact that a liver biopsy specimen taken 22 months prior to death was identical in histologic appearance with sections of the tumor obtained at autopsy. However, the true significance of the biopsy finding was not appreciated, and this patient was regarded as presenting a difficult diagnostic problem during the two years prior to the surgical exploration.

Report of Case

A 19-year-old single white school girl was admitted to the Salt Lake County General Hospital on Dec. 21, 1954, for study of liver disease of several months' duration.

Beginning early in 1953, the patient experienced intermittent generalized pruritus, often so severe that it interfered with sleep. In March, 1954, anorexia and upper abdominal pain were present for several days. In September, 1954, this abdominal distress recurred and was accompanied by a low-grade fever, which continued for one week. A physician found the patient to be jaundiced. The liver was large and tender. Amebic hepatitis was suspected, despite the failure to demonstrate the parasites in specimens of stool. Antiamebic therapy administered during the next three weeks did not produce striking improvement, and the patient subsequently was referred to this hospital for study.

Upon physical examination the vital signs were found to be within normal limits. The patient was well developed and well nourished. There was no jaundice. The upper border of the liver was in its normal position, but the lower edge was felt 9 cm. below the right costal margin. The liver edge was tender and rounded. The spleen could not be palpated. The veins of the abdominal wall were not conspicuous, and there were no spider telangiectases.

The volume of packed red cells was 34%, and the total leukocyte count, 7000 per cubic millimeter, with a normal differential count. The urine contained a trace of protein but no bile. A specimen of stool gave a negative test for occult blood. Blood serologic tests for syphilis were negative. Other estimations included total bilirubin of 0.4 mg. per 100 ml., thymol turbidity, 5 units, and serum albumin, 5.6 gm. per 100 ml., with globulin, 2.7 gm. The prothrombin content of the plasma was 58% of normal. A sulfobromophthalein (Bromsulphalein) test (5 mg. per kilogram of body weight) showed 13% retention after 45 minutes. The alkaline phosphatase was 26 units (King-Armstrong), and the serum cholesterol was 383 mg. per 100 cc. A roentgenogram of the chest showed the right diaphragm to be elevated, but no other abnormalities were seen. No varices could be demonstrated in the esophagus on barium swallow. An oral cholecystogram (double dose) and an intravenous cholangiogram were attempted, but no dye could be visualized in the films. A needle biopsy of the liver was done. The section was interpreted as showing a "fatty liver with bile pigment deposition."

After discharge from the hospital, in December, 1954, the patient remained well until June, 1955, when jaundice returned and persisted until the following December. Reexamination of the patient

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in September, 1955, revealed no new physical finding other than the presence of jaundice. Bile was present in the urine. A paper electrophoretic study of the serum demonstrated a significant increase in the β-globulin fraction. There was no reduction in the albumin component. In December, 1955, the jaundice disappeared. In February, 1956, a large ecchymosis appeared on the left upper thigh. There was no known antecedent trauma. In June, 1956, jaundice again occurred, together with pruritus and constant mild upper abdominal aching pain which was unaffected by respiration. These symptoms persisted and caused the patient to be readmitted to the hospital on Oct. 4, 1956. She still appeared to be well nourished. There had been no loss of weight. Jaundice was evident. There were numerous ecchymoses of the skin, but no spider angiomatas were seen. The liver was felt to be about as large as it had been on the previous admission. The spleen was not palpable, and there was no edema. No other features of the physical examination were remarkable.

The volume of packed red blood cells was 41%; the total leukocyte count was 7700 per cubic millimeter, and the differential count was normal. Some target cells were seen in the stained blood smear. The urine contained bile and a trace of protein. The blood urea nitrogen was 11.5 mg. per 100 ml.; fasting blood sugar, 55 mg., and serum bilirubin, 8.9 mg. in one minute, and 14.6 mg. total. The serum albumin was 5.8 gm. per 100 ml., and the globulin, 3.4 gm. Paper electrophoretic studies again demonstrated that the globulin increase in the serum was primarily in the β-globulin fraction. The thymol turbidity was 7.5 units, and the cephalin-flocculation test was negative. There was sulfobromophthalein retention of 45%. Stool specimens were light tan in color and gave positive tests for occult blood. Radiologic examination failed to disclose evidence of esophageal varices. The prothrombin content of the plasma was 46% of normal, and this did not rise after parenteral therapy with menadione. The exact diagnosis seemed uncertain. Since an incomplete extrahepatic obstruction of the biliary tract could have produced these changes, the patient was subjected to an exploratory laparotomy on Oct. 17, 1956.

Considerable bleeding of all incised tissues was present throughout the operation. A large tumor mass was observed to occupy the major portion of the right lobe of the liver. This tumor was most prominent posteriorly and produced some rotation of the anterior part of the liver toward the left side of the abdomen. No signs of metastasis were present. It was presumed that the mass constituted a solitary primary hepatoma. A cholangiogram was attempted by injection of dye into the gallbladder. Radiographic studies indicated that this dye passed readily into the common duct and into the duodenum but not into the hepatic ducts of the liver. Massive bleeding occurred during the operation, and this was not fully corrected by administration of 3 liters of blood. An attempt was made to excise the right lobe of the liver. Because of the extent of the tumor and because of the bleeding, this resection could not be completed, and the abdomen was closed. Three hours later, the patient died.

Postmortem Examination.—This was performed four hours after death. The pleural cavities and the lungs appeared normal. In the heart there were occasional small pericardial and subendocardial hemorrhages. A hemorrhage was present in the wall of the right atrium. The abdominal cavity contained approximately 400 ml. of blood. The spleen weighed 100 gm. and was unremarkable. No abnormalities were observed in the esophagus, stomach, intestine, kidney, bladder, uterus, ovaries, thyroid, and adrenals. The liver was more than twice the usual size, weighing 4060 gm. The portal vein, hepatic artery, extrahepatic ducts, gallbladder, and common bile duct were normal. The external surface of the liver was smooth. The right lobe was enormous. On cut section, the entire right lobe was found to be replaced by a solitary discrete tumor which was greenish-yellow and lacking in the usual lobular pattern. About most of the tumor there was a distinct connective-tissue capsule. The tumor measured 18 by 15 by 12 cm. and constituted approximately two-thirds of the total volume of the liver (Fig. 1). The portion of the liver not involved in tumor was green and showed the usual lobular markings, and the large bile ducts seen on the cut surface appeared to be distended.

Microscopic examination of the heart confirmed the gross observation of the presence of extensive fresh hemorrhage into the myocardium and epicardium of the right atrial septum.

Multiple sections were made of the tumor and of the unaffected portion of the liver. The cells of the liver tumor were eosinophilic-staining, with finely granular cytoplasm, and were arranged into poorly defined cords or were present as sheets. The nuclei of the tumor cells were small and without prominent nucleoli. In many areas, the tumor cells contained vacuoles of varying size, consisting of sudanophilic material. In patchy areas, there were pigment granules in the liver cells. These did not react positively with an iron stain. Also, in focal areas, there were small amounts of bile-like material lying between liver cord cells as though in bile canaliculi. The tumor cells differed from the liver cord cells of the uninvolved liver in that the adenoma cells had slightly more cytoplasm, which was granular; they contained fatty material in patchy areas, and they were not arranged in a lobular pattern. The cells of the tumor did not show variation in size or in chromatin content.

Fig. 1. — Cut surface, showing circumscribed tumor and adjacent normal liver. A ruler marked in centimeters is included in the figure.

There were no giant cells. All sections from the tumor were free of bile ducts. No evidence of blood-vessel invasion was present. Sections of the margins of the tumor demonstrated a fibrous capsule in which were imbedded islands of normal-appearing liver cord cells and bile ducts. The liver parenchyma away from the tumor was unchanged except for slight periportal fibrosis, with some lymphocytic infiltration. In scattered areas, the cord cells contained pigment (negative with an iron stain), and bile canaliculi in focal areas were distended with bile.

Of signal interest was the discovery that the section from a liver biopsy specimen obtained two years previously was identical in appearance with that of the liver adenoma. In the biopsy, there were no portal triads, and the liver cord cells were granular and vacuolated, as was noted subsequently in the tumor. This biopsy specimen had been examined by a number of persons, none of whom suspected either a regenerating nodule or a tumor. In retrospect, this error seems avoidable.

Comment

No satisfactory clinical diagnosis was established in this patient prior to surgical exploration. Four diagnoses were considered seriously: postnecrotic cirrhosis,[1] "the liver disease of young females," [2] primary biliary cirrhosis,[3] and secondary biliary cirrhosis.

This girl resembled the usual patient with postnecrotic cirrhosis in that she ex-

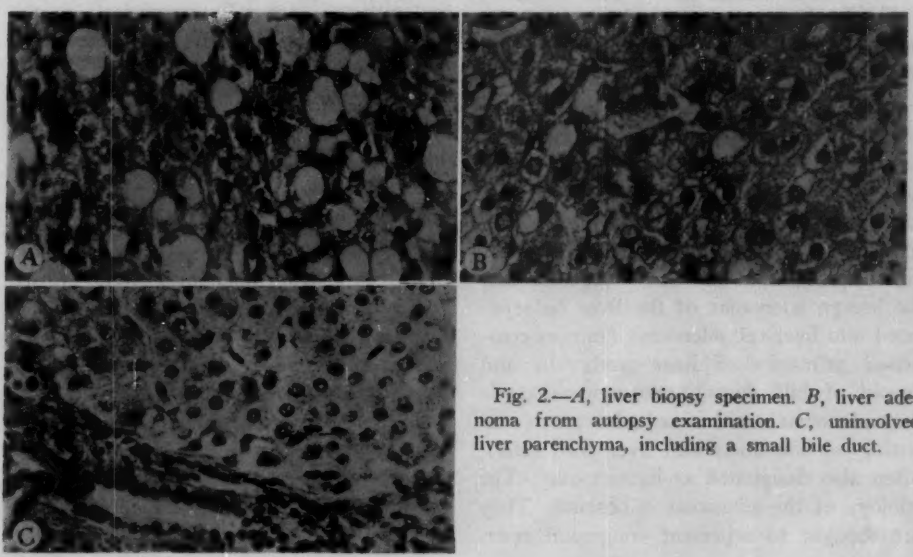

Fig. 2.—*A*, liver biopsy specimen. *B*, liver adenoma from autopsy examination. *C*, uninvolved liver parenchyma, including a small bile duct.

hibited intermittent low-grade fever and abdominal pain. Against this diagnosis was the absence of an acute episode of hepatitis, the pruritus, the elevated alkaline phosphatase, and the increased serum cholesterol. Moreover, the cephalin-flocculation test in this patient was negative, and the thymol-turbidity test was only slightly elevated, whereas both of these tend to be considerably increased in postnecrotic cirrhosis. Finally, in our patient, there was a striking increase in the serum β-globulin, whereas an increase in γ-globulin would be more characteristic for postnecrotic cirrhosis.

This patient likewise did not present many of the findings described under the term "liver disease of young females." The absence of arthritis, of spider telangiectases, and of splenomegaly made this improbable, as did some of the laboratory abnormalities.

The sex, the good nutritional status, the complaint of pruritus, the increased alkaline phosphatase and serum cholesterol, and the elevated β-globulin fraction of the serum suggested the diagnosis of primary biliary cirrhosis. Against this diagnosis was the history of fever and of abdominal pain, as well as the hypoprothrombinemia unresponsive to vitamin K administration.

Finally, by exclusion and because of the fact that it might be amenable to surgery, secondary biliary cirrhosis was considered.

A confusing array of appellations is employed to designate the various types of benign and malignant tumors which are primary in the liver. The tumor described in this case has been termed liver-cell adenoma, hepatocellular adenoma, and benign hepatoma. It has been suggested that the benign adenomas of the liver be separated into liver-cell adenomas (tumors comprised primarily of liver cord cells and devoid of bile ducts), cholangiomas (bile duct adenomas), and mixed adenomas (consisting of bile ducts and liver cord cells), often also designated as hamartomas. The etiology of the adenomas is obscure. They are thought to represent congenital rests. In addition, it has been postulated that they may arise as an area of regeneration at the site of an injury to the liver. In any event, the histologic distinction between so-called benign adenomas and regenerative hyperplasia may be slight or nonexistent.

Benign liver-cell adenomas of the liver are rare. Thus, Warvi [4] collected 62 cases from the literature and added 5 cases. For additional cases and for reviews of the literature, the papers of Christopherson and Collier [5]; Henson, Gray, and Dockerty,[6] and Edmondson [7] should be consulted. Many writers have made no attempt to differentiate between benign and malignant adenomas. It would appear that most of the liver-cell adenomas have occurred in children and in young adults. However, other age groups may be affected. The benign liver-cell adenomas are thought to grow very slowly. Many of these tumors have been found incidentally at surgical exploration. Some of the tumors have made themselves known by the resultant liver enlargement and swelling of the abdomen. In one instance, fatal hemorrhage occurred from such a tumor. Successful surgical extirpation of these adenomas has been achieved in a number of instances. From available literature, it was not possible to find any case clinically comparable to the one described here which was characterized by recurrent jaundice. The dilated bile ducts on the cut surface of the liver and the failure of proximal filling of the bile ducts on the cholangiogram suggest that some degree of compression of the intrahepatic bile ducts may have been produced by the massive tumor.

Grossly, liver adenomas have varied greatly in size and in color. Histologically, they frequently are found to be encapsulated and to be composed of eosinophilic-staining cells with granular cytoplasm, which is greater in amount than in the usual liver cord cell. In many of these tumors, there have been vacuolated cells containing fat and "intracanalicular" bile deposits. It is generally accepted that such

tumors lack the usual architecture of liver parenchyma, having no portal spaces and no central veins. The tumor observed in the patient reported above resembles closely benign liver cord cell adenomas described by others.

Finally, some comment should be made regarding the relationship between benign liver-cell adenomas and malignant adenomas or hepatomas. In some instances, after resection of an apparently histologically benign adenoma, the tumor has recurred and then at times has had the characteristics of a malignant adenoma or hepatoma. This has occurred with sufficient frequency that many observers emphasize that it is not always possible to differentiate histologically between benign and malignant tumors. Certain criteria have been employed to identify malignant change. These include invasion of blood vessels by tumor cells, the formation of satellite nodules, metastases, anaplasia, and tumor giant cells. Clinically, malignant liver-cell tumors tend to run a rather short course, of a few months, although exceptions are noted.

In view of these considerations, it is acknowledged that it is not possible to tell with absolute certainty whether or not the tumor in the patient described in this report is benign or malignant. However, we feel that this case does meet the usual criteria for a benign adenoma of the liver.

Summary

This report concerns the case of a 20-year-old girl who was found to have a large adenoma of the liver. Reasons are given for regarding the tumor as being benign.

Dr. M. M. Wintrobe provided criticism of this manuscript. Dr. William Carnes, Head of the Department of Pathology, made available the pathologic material in this case. Dr. Oscar Rambo prepared the photomicrographs and offered suggestions.

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Survival with Complete Recovery One and One-Half Hours After Clinical Cardiac Arrest

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It has been estimated that sudden unexpected cardiac arrest occurs 10,000 times annually in this country,[1] although resuscitative measures are not undertaken nearly so frequently. However, resuscitation of an arrested heart, whether it is caused by cardiac standstill or ventricular fibrillation, is a common daily occurrence, and so many really dramatic recoveries have been reported in both medical and lay press in recent months that it is no longer of medical importance to add another case to the growing list unless the events were most unusual.[2-11]

We feel that this case is of unusual medical interest because cardiac resuscitation by manual compression was performed 90 minutes after apparent clinical death due to cardiac arrest, when other methods of revival had failed. The patient made a complete recovery without any cardiac or neurologic sequelae and is perfectly normal at the time of this report, which is several months after the dramatic event.

Report of Case

The patient, who was a 69-year-old white woman, was admitted to the surgical service on April 1, 1957, because of severe left-lower-quadrant pain and obstipation of several days' duration. For the past two years there had been intermittent bouts of diarrhea, consisting of 10 to 15 watery stools daily which at times were bloody. This alternated with periods of constipation. A cholecystectomy had been performed 14 years previously, which was complicated by the development of a ventral hernia. High blood pressure was detected approximately six years previously. Examination revealed a rather obese woman with a large ventral hernia in a right-upper-quadrant scar, marked abdominal distention, and exquisite tenderness in the left lower quadrant. The blood pressure was 160/110. A diagnosis of intestinal obstruction involving the sigmoid probably due to an inflammatory lesion was made. The following day a cecostomy was performed for the relief of the obstruction, with use of oxygen and cyclopropane anesthesia. Toward the end of the operation the patient became cyanotic, and the blood pressure dropped to 50/0. The administration of pure oxygen brought a quick recovery. The cecostomy functioned poorly, and a colostomy was decided on. The patient was reoperated on one week later, April 9, 1957, at 1:30 p. m., with use of high spinal anesthesia administered via a rubber catheter. Just as the abdomen had been closed, at 2:15 p. m., the patient became markedly cyanotic and went into shock. The blood pressure and pulse were unobtainable; no heart sounds could be heard, and the patient was considered clinically dead. One of us (M. S.) was making rounds on the medical ward, when an urgent call came for a consultation in the operating room. We ran down one flight of stairs to the operating room and on entering found the patient to be pulseless, with unobtainable blood pressure and inaudible heart sounds. The patient appeared to be dead. Artificial respiration was being maintained by rhythmic compression of the rebreathing bag and an infusion of arterenol in saline had been started. Prior to the operation, the Cambridge Instrument Company's representative had been demonstrating the operating-room cardioscope to the surgical and anesthesia resident staffs. A direct-writing electrocardiograph was attached to the cardioscope, and paper recording was obtainable by the turning of a switch. A glance into the oscilloscope revealed a rapid regular arrhythmia of 200 beats per minute, which was interpreted as a ventricular tachycardia with short runs of prefibrillary beats and ventricular fibrillation (Fig. 1). Because the basic rhythm was considered to be a ventricular tachycardia, it was decided to give the patient procaineamide (Pronestyl) intravenously, with use of cardioscopic control, in an attempt to break the arrhythmia. Fifteen milliliters of procaineamide was given in the next 45

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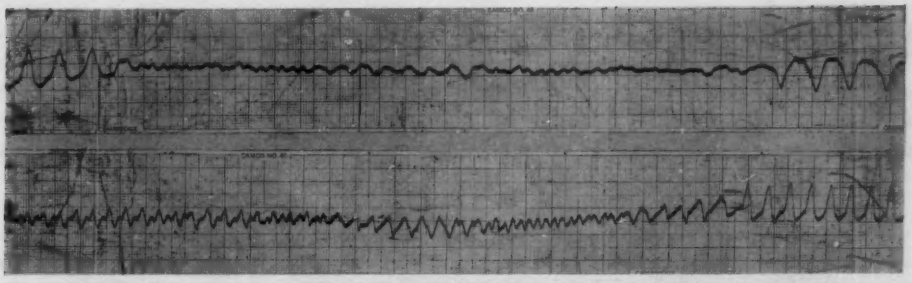
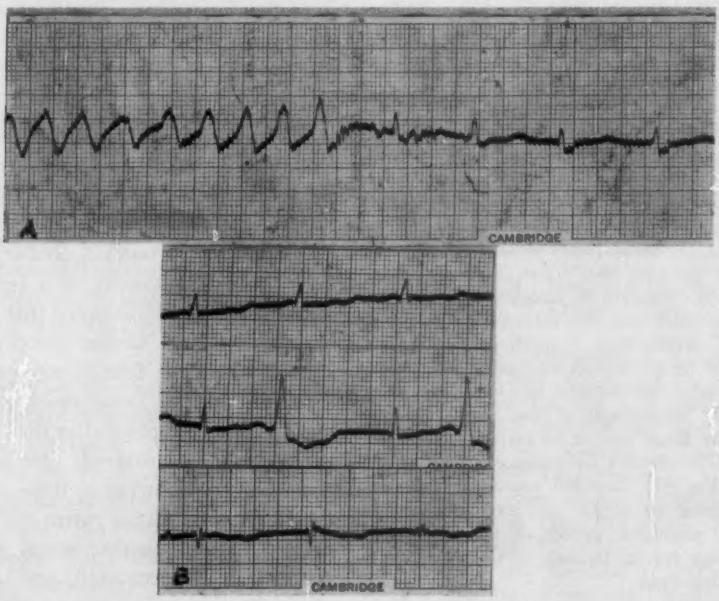


Fig. 1.—The upper strip reveals a ventricular tachycardia with bidirectional beats; in the center of the tracing is a short run of ventricular fibrillation lasting for 9.8 seconds. The lower strip reveals prefibrillary waves, which become a ventricular tachycardia at the end of the strip.

minutes without any change in the arrhythmia. The procaineamide produced a widening of the QRS complexes, and it was discontinued for fear of causing a prolonged ventricular fibrillation. Besides, it was ineffectual. It was then decided to attempt restoration of normal rhythm with the Zoll external pacemaker.[12] The electrodes were attached to the chest at the fourth left intercostal space near the sternal border and at the apex of the heart. The rate of electrical inductions was set at 80 per minute, and the strength gradually increased to maximum. This had no effect on the arrhythmia and did not produce any electrical phenomenon on the heart. These impulses were registered on the electrocardiogram as isoelectric lines. Attempted control with the external pacemaker was maintained for another 45 minutes, and it was decided that the chest should be opened with the thought of using the electrical defibrillating apparatus. An incision was made in the fourth left intercostal space by one of us (S. H.). Observation of the heart revealed no contractions but a twitching motion. Palpation of the heart gave a wriggling impression. Manual compression was begun, and with the second squeeze the ventricular tachycardia was terminated and a sinus rhythm of

Fig. 2.—*A*, this demonstrates the disruption of the ventricular tachycardia and restoration of the sinus rhythm, which is interpreted as of middle nodal origin. This change occurred with the second manual compression of the heart. *B*, Leads I, II, and III, taken about 10 minutes after restoration of sinus rhythm, which is of middle nodal origin. Ventricular extrasystoles may be seen in Lead II.



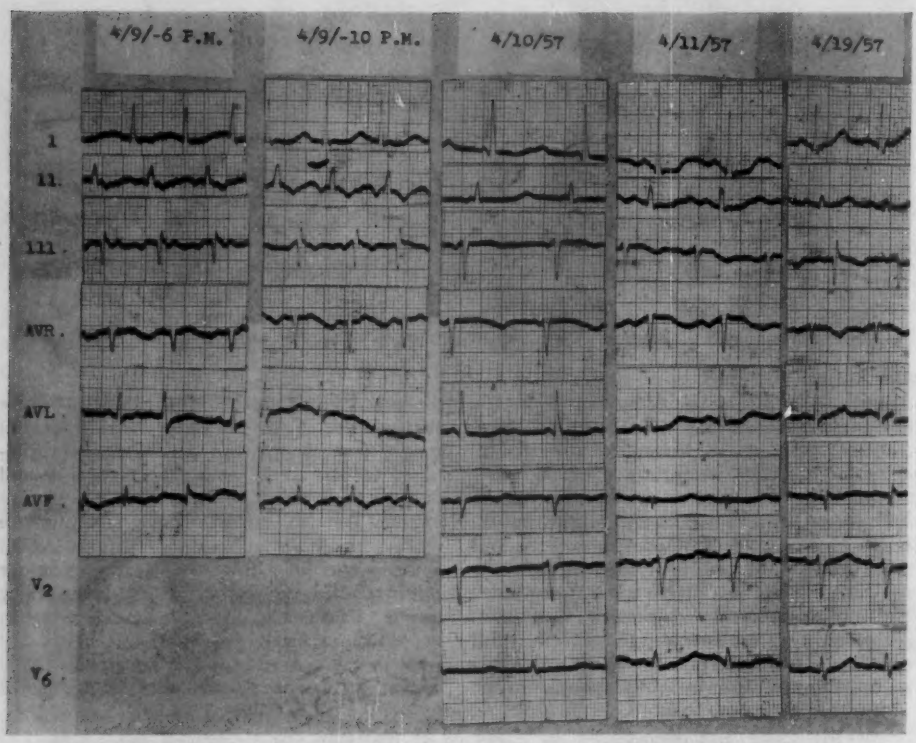


Fig. 3.—Tracings taken at various times up to 10 days after the episode. Normal sinus rhythm without any evidence of permanent myocardial damage is revealed. The changes in Lead aV_F on April 9 and 10 are due to myocardial ischemia.

80 ventricular beats per minute was established. The heart was noted to contract with the onset of this new rhythm which appeared to be of A-V nodal origin (Fig. 2*A*). The heart was kept under observation for another 15 minutes, and, as cardiac contractions seemed well established, the chest was closed (Fig. 2*B*). The blood pressure and pulse had been unobtainable during the entire 90-minute period, but with the establishment of cardiac contractions, the radial pulses became palpable and a blood pressure of 100/75 mm. of Hg was recorded. Approximately 20 minutes after restoration of the heart beat, the patient's eyelids began to quiver, spontaneous respirations began, and twitching of the extremities was noted. The patient was returned to her hospital bed two hours after the manual compression of the heart. Electrocardiograms taken that same evening and subsequent records revealed no evidence of myocardial damage (Fig. 3). Repeated neurologic examinations indicated no mental or neurologic sequelae from the prolonged period of clinical cardiac arrest except for an amnesia as to the events in the operating-room.

Comment

Weinberger and his associates have shown experimentally in dogs that complete arrest of the cerebral circulation for longer than 3 minutes 25 seconds will produce irreversible neurologic sequelae, and because of this fundamental work the 4-minute rule has been applied in human cardiac resuscitation.[13] Cole and Corday, in a report of 132 collected cases, demonstrated that in 78 cases in whom manual cardiac compression was started within the four-minute period, 42% survived, and in those cases where these measures were applied after the four-minute period, only 7% survived. One hundred per cent recovery occurred in those cases where the heart was beating when the chest was opened. Where cardiac arrest was due to standstill, 42% recovered, and in the cases

with ventricular fibrillation, 17% recovered if resuscitation measures were instituted within the four-minute limit.[14]

In the case reported herein we must assume that in spite of the absence of palpatory (pulse) and auditory (blood pressure, heart sounds) signs of vital circulation, which is presumptive evidence of cardiac arrest,[15] adequate perfusion of the brain must have been present, as the patient could not possibly have survived.

The question must be raised as to why a thoracotomy was not done immediately instead of waiting for approximately one and one-half hours.[16,17] One of us (M. S.) felt that since the basic rhythm was a ventricular tachycardia, although short runs of ventricular fibrillation were evidenced, it might be possible to disrupt this rhythm with procaineamide, which of course failed. Zoll [18] states that it does not matter if the basic rhythm is a ventricular tachycardia or a ventricular fibrillation; the clinical picture may be the same in both—that of cardiac arrest. The use of the external pacemaker was doomed to failure from the beginning, for Zoll has pointed out that this instrument will not convert a ventricular tachycardia or ventricular fibrillation to normal sinus rhythm,[18] but this was unknown to us at the time of this episode. He states also that if the pacemaker does not resuscitate the heart within one minute, a thoracotomy should be done.[18]

It is obvious from the experience of others [17,19-21] that the case was not handled properly in many areas. This was due not only to a lack of knowledge but also to a mental inertia which usually occurs when one is faced with this emergency for the first time.

The registration of ventricular complexes on the electrocardiogram does not necessarily indicate ventricular contractions, for these may be recorded for many minutes after cardiac arrest due to standstill.[17,22] One of us (M. S.) recently observed a case of complete heart block in whom ventricular complexes were recorded for 30 minutes after the patient had died during a Stokes-Adams attack due to cardiac standstill. The electrocardiogram may not distinguish whether the cardiac arrest is due to a standstill or to ventricular fibrillation, and a thoracotomy may be necessary to determine the mechanism of the arrest.

The most important lesson learned from this case is that no matter how long clinical cardiac arrest has been present, a thoracotomy must be done and resuscitative measures pursued, for vital circulation may be present in the absence of clinical evidence.

Conclusion

A case of clinical cardiac arrest due to ventricular tachycardia with short runs of ventricular fibrillation is presented in which resuscitative measures consisting of the administration of intravenous procaineamide and the application of the Zoll external pacemaker were attempted for one and one-half hours without success. The chest was finally opened, and after the second manual compression of the heart, sinus rhythm was established, with restoration of cardiac contractions. The patient made a complete recovery, without neurologic sequelae.

It is emphasized that no matter how long clinical cardiac arrest has been present, a thoracotomy should be done and manual compression instituted, for vital circulation may have been maintained in the absence of clinical signs.

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Poliomyelitic Paralysis of Deglutition—Upper Esophageal Achalasia

Report of a Case of Twenty-Seven Months' Duration with Recovery

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Impaired deglutition caused by motor paresis resulting from bulbar poliomyelitis is in most cases due to a lesion of the motor nevron of the cerebral nerves which cooperate in the act of swallowing (Nerves VII, IX, X, XII). This type of paralysis is seldom permanent, except in patients with widespread bulbar lesions. A permanent isolated paralysis of deglutition is a rare finding and might indicate that some other mechanism is responsible. The act of swallowing is a complex function, involving both streaked and smooth muscles and supplied by autonomous nerves as well as nerves controlled by will.[1] The act of swallowing in the lower section of the pharynx consists of a series of accurately synchronized contractions occurring in rapid succession. In connection with the following referred case, the "mouth of esophagus" is of special interest. This functionally independent ring muscle which consists of the lower transverse fibers of constrictor pharnygis superior was first described by Killian.[2] Its function has since been closely investigated.[3] When not engaged in the act of swallowing, the upper end of the esophagus remains contracted. Normally the upper end of the esophagus relaxes at the termination of the act of swallowing, with a simultaneous contraction of the pharynx and closure of the larynx. Under pathologic conditions a disturbance of the synchronization may occur whereby the relaxation takes place too late, too early, or not at all. The condition may be comparable to the well-known achalasia esophagi, where the functional obstruction is situated in the lower end of the esophagus. Faulty deglutition on this basis has previously been discussed.[4,5] As a sequence of poliomyelitis, such a disturbed function may have been present in two cases previously described,[6,7] and a disturbance of coordination of this nature is assumed to be responsible for the dysphagia in the case described here.

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From the Medical Department B, University of Bergen.

Report of Case

The patient, a boy born in 1948, was admitted in September, 1953, to Medical Department B, University of Bergen, for bulbospinal poliomyelitis. Upon admittance he was cyanotic and in a state of shock. After tracheotomy and artificial positive-pressure respiration his condition quickly improved.

Examination revealed pronounced paresis of the muscles of the throat, shoulders, and diaphragm; moderate paresis of intercostal musculature, back musculature, and abdominal musculature, and somewhat more pronounced paresis of the hip muscles. The musculature of the extremities was only slightly affected. A slight right facial paralysis, bilateral pharynx paralysis with palate deviation to the left, paralysis of both sides of the sternocleidomastoideus muscle and a slight right deviation of the tongue were found in the cerebral nerve area. The pareses receded quickly. After three weeks the patient's ability to breathe was satisfactory, and he was removed from the respirator. After three months the patient was allowed up. After a further year only a trace of paresis was found in the musculature of the trunk and extremities, and the patient could hold his own in play with children of his own age, with one exception—he was unable to swallow.

Examination of the cerebral nerves revealed moderate palate deviation toward the left, almost total atrophy of right sternocleidomastoideus, considerable reduction in strength of left sterno-

cleidomastoideus and paresis of atrophy of upper sections of the trapezius muscle. In attempts at swallowing, seemingly normal deglutitory movements were observed, with the larynx rising strongly. On completion of the act of swallowing, bolus could be seen gathered in the hypopharynx, while attempts at swallowing larger portions caused fluid to run over the edge of introitus laryngis, which led to coughing. The patient had to be tube-fed. In view of the risk of aspiration, the tracheotomy tube had to be retained. By degrees, however, the patient taught himself to clean his pharynx of secretion and spit it out. This eventually also occurred in his sleep, so that after two years we were able to remove the tube and close the tracheostoma. The patient was also taught how to tube-feed himself. He attended school in the normal way and fed himself during breaks. There was still not the least sign of a passage through the esophagus. A further examination, however, revealed a strange fact. At an x-ray examination, when an attempt was made to swallow contrast material, it was seen to slip at the lower part of the hypopharynx on a level with the upper end of the esophagus. The hindrance of the passage here appeared to be considerable, since at screening movements of deglutition were seen to occur with great force, pressing the contrast material down toward the bottom of hypopharynx with such pressure that some was regurgitated up in the epipharynx. A sound was guided into the esophagus, and with retrograde filling good peristaltic movement was seen in the esophagus up to the level of the larynx. No permanent obstruction of the passage, however, could be demonstrated there. An esophagoscope passed unhindered from the hypopharynx to the esophagus, and one had the impression that as a rule there was no obstruction in the passage during tube-feeding. It was, however, noticed that when the patient led the sound into the esophagus, he always expired deeply. If he did not, the sound met with resistance at the lower end of hypopharynx. Such a hindrance also arose if, while conducting the sound, the patient made an involuntary swallowing movement. These facts led to the decision to wait and not resort to operative treatment, which had been considered.

On Nov. 12, 1955, after 27 months' exclusive tube-feeding, the patient's swallowing mechanism was reestablished, first for spitting and then, after a few weeks, for the intake of all kinds of food.

Comment

The patient suffered from a complete inability to swallow which arose as a result of bulbospinal poliomyelitis and was of 27 months' duration. With the demonstrated affection of nucleus ambiguus in mind, it was natural to assume that the present condition was one of paralysis of the deglutition sensu strictiori, namely, a paralysis of the muscles which activate the process of swallowing. Examinations revealed, however, that the motions of swallowing proceeded apparently normally and with normal force, yet without being able to effectuate any passage from the hypopharynx to the esophagus. The dysphagia appeared to be due to a hindrance in the region of the "mouth" of the esophagus, either an organic stricture or a functional spasm. Such a hindrance could be demonstrated only during the act of swallowing. An esophagoscope and sounds passed unimpeded. The spasm must therefore have been temporary and have occurred during the actual act of swallowing. This deduction was supported by the observations made during the passing of the sound: during expiration the sound did not encounter any resistance, but if the patient did not expire or if there was an involuntary act of deglutition the sound, as a rule, met with an often insurmountable resistance in the lower section of the hypopharynx. It seemed as though the patient had acquired a means of relaxing the "mouth" of the esophagus. During expiration with open larynx the upper end of the esophagus was relaxed; during an attempt to swallow with closed larynx, evidently a simultaneous contraction of the upper end of the esophagus also took place. The patient's unability to swallow was therefore not due to paralysis of deglutition in the accepted sense but to a disturbed coordination—a disturbance of the normal synchronization of the swallowing motions.

In the introduction of this paper, synchronization of swallowing motions is touched upon. This complicated mechanism seems to presuppose a coordination "center" for the act of swallowing. The assumption that such a center exists, although not anatomically established, is based upon observations of patients with disturbances in the act of swallowing similar to those of our

patient. A poliomyelitis-damaged swallowing coordination "center" is thus assumed to be responsible for the impaired deglutition in two apparently similar cases.[8]

Treatment

Where disturbances in swallowing similar to those in our patient have been present, operative treatment consisting of section of the cricopharyngeus muscle has been attempted,[7] and also neurectomy and myectomy have been considered.[8] Experience from our case, where completely normal deglutition was established after 27 months conservative therapy, in our opinion speaks for exercising restraint in the use of such interventions.

Summary

A report is given of a case of postpoliomyelitic paralysis of deglutition in a 5-year-old boy, interpreted as being the result of a poliomyelitis-damaged swallow coordination center. The inability to swallow was complete, necessitating tube-feeding for 27 months, after which a normal swallowing function was spontaneously reestablished. The case illustrated that a long period of conservative treatment is indicated in such conditions before attempting surgical intervention.

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Treatment in Internal Medicine

Therapy of Strongyloidiasis with Dithiazanine

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Introduction

Data presented in this paper provide evidence of the anthelmintic activity and therapeutic effectiveness of 3,3′-diethylthiadicarbocyanine iodide (dithiazanine, Compound 01748) against Strongyloides stercoralis infections in humans and experimental infections with Strongyloides ratti in rats. Prior to this study, a large number of other drugs were evaluated by us for anthelmintic activity against murine and human strongyloidiasis. None of the compounds employed in our previous investigations gave evidence of significant activity or cure of strongyloidiasis in either host. There is a definite need for effective therapeutics for strongyloidiasis. Stoll [1] estimated that there were approximately 35,000,000 infections with S. stercoralis in the world. In one hospital in New Orleans in recent years there have been several hundred patients with strongyloidiasis. Jones [2] has described precisely the clinical significance and characteristics of strongyloidiasis. Frequently the infection persists for many years in man, and on rare occasions it may prove fatal.

Interpretation of the results of therapy for strongyloidiasis based upon examination of stools alone is likely to be misleading. Final determination of the efficacy of drugs against strongyloidiasis should be based upon examination of a series of stools and duodenal fluids.[3] Therefore, in the present study, the criteria for therapeutic effectiveness were based upon the examination of both duodenal fluids and of numerous stool specimens after treatment. In addition, a more conclusive criterion was employed to evaluate the anthelmintic activity of dithiazanine and to supplement the data obtained from the treatment of human strongyloidiasis. Autopsies were performed on rats infected with S. ratti, which had been treated with the same drug as employed in humans, in order to determine whether or not infection persisted in the intestine after chemotherapy, despite the disappearance of diagnostic stages of the parasites from the stools.

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The drug employed in this study, dithiazanine (compound 01748), was provided by Eli Lilly and Company.

The statements and conclusions published by the authors are the results of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

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I. Chemotherapy of Experimental Murine Strongyloidiasis

Methods

Twenty-three rats were infected with a strain of S. ratti which was isolated originally from wild rats in New Orleans in 1949 and maintained in black pied rats since that time. The animals weighed from 200 to 250 gm. Seventeen rats were treated with a suspension of 3,3′-diethylthiadicarbocyanine iodide by gavage. A 0.5 cc. amount of the suspension containing 10 mg. of the anthelmintic was intubated into the stomach twice daily for seven days. The drug was administered by means of a small rubber catheter attached to a syringe. A total of 140 mg. of the compound was given during a complete course of therapy. The treatment was initiated on the sixth day after inoculation, at which time large numbers of embryonated eggs and larvae of S. ratti were demonstrable in the excreta of the animals.

The remaining animals, which were given inoculations on the same date as the treated rats, served as untreated controls in order to detect any evidence of spontaneous loss of infection during

the same period of time that their littermates were receiving medication. Experience with a few thousand rats infected with this strain of S. ratti has shown that the patent period in untreated animals exceeded considerably the seven-day treatment period employed in this study. Also, hundreds of rats have been treated with other compounds, with similar technique, without producing elimination of infection.

The stools of all of the rats were examined daily during the course of medication. Direct fecal smear and formalin-ether-concentration techniques were employed routinely.

The animals were killed on the day after completion of therapy. A portion of the small intestine, approximately 8 to 10 in. in length, starting just above the pylorus, was removed. This area is the site of predilection of the adults of S. ratti. The segment of bowel was opened, and the mucosa was removed by scraping. The mucosal scrapings were placed in distilled water in a Petri dish and incubated at 37 C for two hours to permit the tissue to undergo autolysis. The autolysis of the tissue frees the worms, if present, and facilitates their detection. This procedure had been used by us effectively for several years to collect viable adult female S. ratti for biochemical studies.

Results

Infection with S. ratti was eliminated in all 17 rats which were treated with 3,3′-diethylthiadicarbocyanine iodide. No eggs or larvae could be demonstrated in the excreta of the rats during the final part of the course of treatment. No adults, eggs, or larvae could be found in the autolyzed mucosal scrapings of all 17 rats which were killed after completion of therapy. The infections persisted in all of the untreated control animals. Eggs and larvae usually were no longer demonstrable in the stools after eight doses of dithiazanine or four days of medication. The earliest that the eggs or larvae of S. ratti could not be found in the excreta of the rats was after six doses, or three days of therapy. One rat was killed after 10 doses. No adult organisms could be detected in the autolyzed mucosal scrapings of this animal. Occasionally, dead adult female S. ratti were observed in the stools of rats during treatment.

The stools of the rats which received medication were colored blue or blue-green. This cyanine dye had no apparent affect on the viability or motility of embryonated eggs and rhabditiform larvae of S. ratti which were present in the excreta during the first three or four days of treatment. This excludes the possibility that negative stools during or after treatment resulted from action of the drug on the larvae rather than on the adult worms.

Examination of the intestine of the rats killed after treatment revealed considerable variation in the staining. In most of the animals, 30% to 100% of the small intestine was discolored by the dye. The mucosa in these areas had a light green or blue color. Small areas which were dark blue were scattered throughout the less deeply stained portions of the bowel. The large intestine invariably was intensely stained by the dye.

An incidental observation was the disappearance of eggs of Hymenolepis nana and of Syphacia obvelata from the stools of two rats during treatment. No adults of the above species of helminths could be found after therapy during a careful search of the entire intestine of these rats.

II. Chemotherapy of Human Strongyloidiasis

Methods

Eighteen patients with S. stercoralis infection were treated with dithiazanine. Initially, a dosage schedule of 200 mg. of the compound three times daily, given approximately two hours after meals for five days, was employed. Later, the treatment period was extended to 21 days for two reasons. First, it became obvious that treatment for five days was inadequate in some, but not all, cases. Also, it was thought that an increase in the duration of the treatment period might reduce or eliminate the influence of hyperinfection or internal autoinfection, if present, on the therapeutic results. If developing parasites were in the circulatory phase at the initiation of treatment, the possibility that they would be exposed to the anthelmintic would be enhanced by a longer treatment regimen. Sixteen of the patients received the anthelmintic in the form of the 100 mg. enteric-coated tablets designed to release the drug after passage through the stomach. Two persons were given a cherry-flavored suspension which contained 20 mg. of the drug per cubic centimeter.

All of the patients were men. Some of the persons had signs and symptoms compatible with clinical strongyloidiasis. Others had no complaints or findings referable to the abdomen or gastro-

*Cases of Strongyloidiasis Treated with Dithiazanine**

Case No.	Pretreatment		Days of Treatment	Total Dosage, Gm.	Posttreatment		Duration of Follow-Up, Wk.	Reactions During Treatment	Treatment Failure
	Stools	Duodenal Drainages			Stools	Duodenal Drainages			
1	Pos.	Neg.	5	3.0	21 neg.	1 pos.	5		Yes †, No
1a	Neg.	Pos.	21	12.6	14 neg.	4 neg.	15		No
2	Pos.	Pos.	21	12.6	6 neg.	1 neg.	12		No
3	Pos.	Pos.	5	3.0	11 neg.	3 neg.	17		No
4	Pos.	Pos.	21	12.6	13 neg.	3 neg.	12	Diarrhea	No
5	Pos.	Pos.	21	12.6	11 neg.	4 neg.	6		No
6	Pos.	Pos.	6	3.6	13 neg.; 2 pos.	1 pos.	8		Yes ‡
7	Pos.	Pos.	21	12.6	13 neg.	4 neg.	12		No
8	Pos.	Pos.	5	3.0	5 neg., 1 pos.	2 pos.	8		Yes †, Yes
8a	Pos.	Pos.	21	12.6	----	1 pos.	3		
9	Pos.	Pos.	5	3.0	13 neg.	1 neg.	11		No
10	Pos.	Pos.	5	3.0	2 pos.	1 neg.	1		Yes †, No
10a	Pos.	Neg.	5	3.0	5 neg.	1 neg.	3		
11	Pos.	Pos.	8 §	4.8	33 neg.	7 neg.	24	Diarrhea	No
12	Pos.	Pos.	21	12.6	26 neg.	4 neg.	12		No
13	Pos.	Neg.	5 §	3.0	13 neg.	3 neg.	11		No
14	Pos.	Pos.	21	12.6	17 neg.	3 neg.	9		No
15	Pos.	Pos.	21	12.6	6 neg.	3 neg.	7		No
16	Pos.	Pos.	21	12.6	14 neg.	2 neg.	3		No
17	Pos.	Pos.	21	12.6	14 neg.	2 neg.	5		No
18	Pos.	Pos.	21	12.6	11 neg.	1 neg.	4	Vomited (2X)	No

* In all cases (1) patients were men; (2) dosage was 200 mg. t. i. d.; (3) urinalyses, hemograms, liver profile, and BUN showed no significant change during or after treatment.
† Re-treated.
‡ Treatment discontinued due to another illness.
§ Suspension (all others received enteric-coated tablets).

intestinal tract. In some cases the S. stercoralis infection was complicated by or coincidental to other diseases.

Since all of the persons in this series were hospitalized for weeks or months, it was possible to perform extensive laboratory studies on the urine, blood, and duodenal fluid. The procedure described below was followed, insofar as possible, for each patient.

Urinalyses were performed at least twice before treatment, on the third and seventh days of medication, and after completion of therapy. BUN determinations were done one or more times before treatment and repeated at weekly intervals. Hemograms were performed prior to therapy, once on the third day of medication, and weekly thereafter. Liver-profile studies were made at least one time before chemotherapy and then once weekly during the period of hospitalization. The procedures for assessment of liver function included determination of bilirubin, of zinc-lipid-thymol turbidities, of alkaline phosphatase values, and of the prothrombin time.

An effort was made to obtain stools daily, or at frequent intervals, before and after therapy, while the patients were hospitalized. Direct fecal smear and formalin-ether centrifugal-concentration techniques were employed on all stools. Formalin-preserved fecal specimens were submitted by some patients after their discharge from the hospital as part of an extended post-treatment examination routine.

Duodenal drainage was performed on all cases prior to treatment in an attempt to obtain at least one specimen of duodenal fluid which was positive for rhabditiform larvae. Each specimen of duodenal drainage fluid was examined microscopically at length by three persons proficient in the diagnosis of strongyloidiasis by this technique before it was considered negative for parasites. Since the procedure for duodenal drainage is arduous and uncomfortable for some patients, it was not desirable to repeat it beyond a reasonable number of examinations after treatment. However, all patients submitted to from one to seven post-treatment duodenal drainages.

On a number of occasions additional techniques were employed to supplement and serve as a check on the above routine procedures. Some stools in which larvae could not be demonstrated by direct smear and formalin-ether concentration techniques were examined by the zinc sulfate centrifugal-flotation method. A few fecal samples were cultured in bone charcoal. Some duodenal drainage fluids which yielded no larvae by direct microscopic study were digested with Chlorox (sodium hypochlorite solution). The resultant sediment of the digest obtained by centrifugation was examined. None of the above procedures elicited larvae when they were not demonstrated by the routine procedures.

Results

Diagnostic forms of S. stercoralis were not demonstrable after therapy in stools and duodenal drainage fluids of 16 of the 18 treated patients. The cure rate in this series was 89%. Two of the sixteen cases were retreated for 5 and 21 days, respectively, with evidence of elimination of infection. One of the two cases which were listed as treatment failures received medication for

only six days. Treatment was discontinued because of the psychiatric status of the patient, which was unrelated to therapy. Only one of the patients who received treatment for 21 days had evidence of parasitism after treatment.

Fifty-two duodenal drainages were done on the 18 patients during and after treatment, and forty-seven, or 90%, of the fluids contained no demonstrable larvae or eggs of S. stercoralis. Larvae of S. stercoralis could not be found in 259, or 98.5%, of 264 stools examined after treatment. Diagnostic stages became extremely difficult to find in the stools and drainages of the two cases which were considered treatment failures. One patient who was treated for eight days has had 7 negative post-treatment duodenal drainages and 33 negative post-treatment stools over a period of six months after therapy. The numbers of negative stools after therapy ranged from 5 to 33 in the series of 18 patients.

The dye had no apparent effect on the motility of the rhabditiform larvae of S. stercoralis in the deeply stained stools when the larvae were still present during the first few days of therapy. This would indicate, as in S. ratti infections in rats, that the drug is active against the adults and that the absence of larvae in the stools does not result from a direct action on the larvae.

Two patients had mild and evanescent diarrhea, without cramping, during therapy. Two patients noted an increase in bowel movements without diarrhea. One patient vomited twice during a 21-day course of therapy. The medication imparted a blue color to the stools. This served as a check on the release of the dye from the tablets and on the proper administration of the drug. The results of urinalyses, hemograms, BUN determinations, and liver-function studies revealed no significant change in any of the patients. Clinical improvement was obvious in some cases; however, since some of the patients had no symptoms attributable to the parasitic infection or had other diseases, no assessment of clinical amelioration was attempted. Additional details concerning the study are presented in the Table.

Summary

Dithiazanine (3,3′-diethylthiadicarbocyanine iodide) is an effective therapeutic agent for strongyloidiasis. The infection was eliminated in 89% of the patients treated with this anthelmintic. The rigid criteria for cure included examinations of a series of stools by several techniques and of post-treatment duodenal drainage fluid from each patient. The dosage of dithiazanine which was employed in most of the cases was 200 mg. three times daily for 21 days. The side-reactions to therapy were infrequent, mild, and evanescent. Evidence of the high therapeutic efficacy of this new anthelmintic against Strongyloides stercoralis was supplemented by observations of the effect of the drug on Strongyloides ratti infection, the experimental murine counterpart of human strongyloidiasis. There was elimination of infection with S. ratti in 100% of the rats treated with this same compound, based upon both stool and autopsy examinations of the animals.

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Evolution of Modern Medicine

The Development and Meaning of the Hyphenated Eponym in Medical History

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The double eponym is a recent invader of medical literature because of the individual nature of medical discovery before the early years of the 19th century. The titans of medicine—Hippocrates, Galen, Vesalius, Harvey, Morgagni, Sydenham, Heberden, Corvisart, Laënnec, and Trousseau, to name but a few—were solo investigators and writers. Even William and John Hunter did not collaborate, except that William was assisted in a minor way by his brother in the delineation of the maternal and fetal circulations. In fact, years later John picked a public quarrel with his older brother over a quibble about priority. Although the medical giants developed schools and surrounded themselves with students and assistants, they were scientifically many heads taller than their auditors.

Evidence of medical collaboration appeared first in the persons of the three Weber brothers of Wittenberg. In 1825, Ernst Heinrich Weber, professor of anatomy and physiology at Leipsig, with his middle brother, Eduard Friedrich Weber, measured for the first time the velocity of the pulse wave and disproved Bichat's theory that the pulses were synchronous in all arteries. Twelve years later, they compared the flow of blood and lymph. In 1845, they reported their major discovery, the inhibitory power of the vagus nerve. The middle brother collaborated also with his younger sibling, Wilhelm Eduard Weber, professor of physics at Göttingen for 60 years, who constructed the first electromagnetic telegraph. They published in 1836 their classic study of the mechanics of human joints and locomotion.

Today, the unwary reader reasonably assumes that the hyphen coupling the names of a medical eponym signifies some type of collaboration. However, such is usually not the case. An examination of the variety of relationships inflicted by the hyphen upon the partners of the double eponym is the purpose of this excursion into eponymology.

At the outset, clarity is served by discarding from consideration what might be termed the false diploeponym. In part, this category is generated by the continental custom of using the hyphenated names of one's parents for one's own surname: Riva-Rocci, Brown-Sequard, Krafft-Ebing, Price-Jones, Magnus-Levy, Smith-Petersen, Albers-Schönberg, Duran-Reynals, Watson-Jones, Denny-Brown, and Szent-Györgyi. Another segment of this category comes from discoveries memorialized by men whose first and last names in speech and print resemble surnames: Austin Flint, Graham Steell, Parkes Weber, Argyll Robertson, Ramsay Hunt, and Foster Kennedy. The student is sometimes confused by a *trompe l'oeil* created when the editor blue-pencils in a hyphen where the double name of the discoverer is affixed to his discovery. Thus, H. Bence Jones, as everyone knows, discovered Bence-Jones proteinuria. Merely as an aside, it must be recalled that the HeLa (sans hyphen and sans space) tissue-culture strain does not bear an oriental

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eponym; the letters are abbreviations of the first and last name of the unfortunate donor of the malignant cells. Not echolalia, but the only fraternal diploeponym extant, the Hailey-Hailey disease, signifies benign chronic familial pemphigus.

This discussion of hyphenated eponyms will limit itself to those in common usage. No claim is made for completeness; a prejudice for internal medicine is admitted. Nothing is to be gained by unravelling rarities like the Johnson-Taylor disease, a dermatitis caused by contact with the blood of the wild cottontail rabbit. Likewise, little can be gotten from double eponyms that have disappeared in the wake of specific pathological terminology, such as the appropriate replacement of Minkowski-Chauffard anemia by congenital hemolytic anemia and Hayem-Widal anemia by acquired hemolytic anemia. Some diploeponyms have become useless as medicine advanced. For example, the Schultz-Charlton reaction, formerly so helpful in the diagnosis of scarlet fever, is all but forgotten since the frequent use of penicillin. All too rarely, one name and the hyphen of a coupled eponym are amputated. Some 75 years ago what we call Horner's syndrome was spoken of as the Bernard-Horner syndrome, because Claude Bernard had produced it experimentally in animals before Horner described it in man. Similarly, the Wassermann test for syphilis was known in its early days as the Bordet-Wasserman reaction, since Bordet (with Gengou) had discovered the complement-fixation reaction. In less recent literature, the Widal test for typhoid fever was written as the Gruber-Widal reaction, because Gruber's observation that agglutination was specific was adapted by Widal. The currently popular Sjögren syndrome was formerly called the Gougerot-Sjögren syndrome, being described first in 1925 by the French dermatologist. From 1933 to 1950, Henrik Sjögren, a Swedish ophthalmologist, wrote 10 papers on the sicca syndrome. It seems only proper that this eponymic jawbreaker, born to be mispronounced, should be blessed with amputation at the hyphen.

The hyphen often signifies independent discovery, occasionally in the same city, but not actual collaboration. Although Adams succeeded Stokes as Regius Professor of Medicine at Dublin, they separately described in different journals 19 years apart the syncope we designate the Adams-Stokes syndrome. Stokes later acknowledged in print to the deceased Cheyne, another fellow-Dubliner, the prior description of periodic breathing now known as Cheyne-Stokes respiration. Many times, however, the hyphenated names are from different continents. The focal embolic nephritis in subacute bacterial endocarditis is known as the Löhlein-Baehr lesion, the two independent investigators being separated by two years and the Atlantic ocean. A similar distance and time isolated the descriptions of the pathognomonic cell in Hodgkin's disease by Sternberg and Dorothy Reed. Charcot and Marie, in February, 1866, distinguished five cases of progressive muscular atrophy that involved only the legs. Across the British Channel, Henry Howard Tooth later that year independently wrote his Cambridge thesis on "the peroneal type of progressive muscular atrophy," which has since been known as the Charcot-Marie-Tooth syndrome. An aura of unusual coincidence envelops the Brailsford-Morquio coupling. Observations on chondro-osteodystrophy were independently published in 1929 by the Englishman in an American journal and the Montevidean in a French journal.

Frequently the hyphen signifies the link between a discoverer whose diligent search through the literature reveals that he is only a rediscoverer. The Budd-Chiari syndrome of hepatic vein obstruction was described by Budd, in 1857, and redescribed by Chiari, in 1899. The years intervening need not be so great. Waterhouse in 1911 added his case to 15 in the literature and synthesized a clinical picture of adrenal hemorrhage complicating meningococcus meningitis; Friderichsen, in 1918, earned his hyphenage by

writing the second major compilation of the subject. Or the intervening years may be greater. Baumgarten became hyphenated with Cruveilhier to designate the abdominal venous hum in portal hypertension after a span of 72 years. The word infantilism appeared in 1871 in Paul Lorain's preface to a student's Paris thesis on retarded development in tuberculosis. Subsequently, in 1908, the term was restricted to hypopituitarism by E. Levi; hence, the eponym Levi-Lorain, known to all medical students and witnessed by practically none. Only recently Jeghers revived Peutz's obervation of two decades earlier that oral pigmentation often accompanies congenital intestinal polyposis. At times, the hyphen represents a piece added to the jig-saw puzzle of a syndrome. Arnold, in 1894, described a single case of an abnormality of the cerebellum; two years later Chairi reported 21 cases and delineated the two major types of the Arnold-Chiari deformity. Von Hippel described a small hemangioendothelioblastoma of the eye. Lindau later pointed up its association with cerebellar tumor, the Lindau-von Hippel syndrome.

Occasionally, the hyphens become multiple, more years pass, and others act as midwives-in-eponomy. Such is the case of the Lawrence-Moon-Biedl syndrome. The first two described the disorder in 1866, but it was forgotten. Since Bardet had made the malady the subject of his Paris thesis, in 1920, it became known as the Bardet-Biedl syndrome after the latter published cases in a brother and sister in 1924. Justice and parturition were accomplished in 1925 by the reestablishment by Solis-Cohen and Edward Weiss of the true priority and the well-known triple eponym. To be just to all involved, this familial idiocy should be idiotically d e s i g n a t e d the syndrome of Lawrence-Moon-Bardet-Biedl-Solis-Cohen-Weiss, seven names for six discoverers. Without doubt, the most populous multiple eponym for the smallest possible innovation is the addition of a single suture by Finsterer to the closure of a modification of the Billroth I gastric resection, which has been named the Finsterer-Kocher-Von Haberer-Finney-Billroth procedure.

Eponyms, like rank weeds, unfortunately spring up even when the authors specifically defined their observations in scientific terminology. Although Adolf Kussmaul and Rudolph Maier together described periarteritis nodosa, in 1866, and actually used the term many times in their paper, a well-known system of medicine lists as synonyms for the disease "Kussmaul's disease and Kussmaul-Maier disease," despite the discoverers' sincere antieponymic efforts. A contemporary example concerns Zollinger and Ellison, who in 1955 called attention to the ulcerogenic tumor of the pancreas. Eiseman and Maynard titled their paper on the subject "a non-insulin producing islet-cell adenoma associated with progressive peptic ulceration [the Z o l l i n g e r-Ellison syndrome]."

Some eponyms, even triple ones, remain current in medical speech and writing because they are briefer and more easily learned than the medical terminology. Three instances that come easily to mind are the Weber-Christian disease (relapsing febrile nodular nonsuppurative panniculitis), the Rendu-Osler-Weber disease (familial recurrent epistaxis with telangiectasia), and the Stevens-Johnson syndrome (erythema multiforme exudativum major).

Eponyms are often historically determined by the genesis of a specialty in medicine, of which neurology is a classic example. The first *Lehrbuch* of neurology was published in Germany, in 1846, by Mortiz Romberg. Charcot with his pupil Marie, in Paris, and Duchenne, in Boulogne, established the specialty in France. In England, Hughlings Jackson, Gowers, and Horsley were at work. These men had active associates, assistants, and students, whose names have been hyphenated and intertwined to make the multiple and various couplings that constitute the eponymic forest of neurologic disorders. To become lost in this forest would indeed be not seeing it for the trees. The develop-

ment of general surgery is likewise marked by the names of pioneers and their followers, each modification of an operative procedure serving as the birth of another diploeponym. These range alphabetically from the Ammon-Agnew plastic operation on the canthus to the Wilson-Longmire cholangiojejunostomy. The literature of dermatology is a veritable who's-who-who's-who.

Priority does not always assure top billing in double eponyms. Ebstein has priority over Pel by 79 pages in the 1887 *Berliner klinische Wochenschrift* in the description of what they termed chronic relapsing fever, a new infectious disease. Later, both men became convinced that the cases they had described were Hodgkin's disease with a relapsing character to the fever. The diploeponym Pel-Ebstein took hold. The Marie-Strümpell eponym for rhizomelic spondylitis should have the names reversed, since the latter's paper appeared a year before the former's. Neither knew that the Irish prodigy of the 17th century who died at 32, Bernard Cannon, wrote his M.D. thesis at Rheims on ankylosing spondylitis. In 1859, Landry described a symmetrical ascending paralysis. Osler, in an early edition of his textbook, described similar cases as acute febrile polyneuritis. Today, the disease is considered an infectious neuronitis and bears the diploeponym of Guillain-Barré for the discoverers of the albuminocytologic dissociation in the spinal fluid. Haymaker and Kernohan have attempted to do historical justice by entitling their monograph "The Landry-Guillain-Barré Syndrome." Francois-Amilcar Aran has eponymic priority in the Aran-Duchenne type of progressive muscular atrophy, but the cases he published were studies of clinical and pathological material collated by Duchenne. The precedence in one hyphenated eponym seems to be governed more by euphony than by priority. Thus, although the dove-coo murmur was described by Key, in 1827, and two years later by Hodgkin, the rhyme has perpetuated the bruit de scie of Hodgkin-Key.

Although it is reasonable to expect a place in an eponym for an early writer, a spot near a hyphen should certainly be reserved for the elucidator. That this is not always so, the Hand-Schüller-Christian syndrome demonstrates. Schüller, in 1915, and Christian, in 1919, correlated a syndrome of defects in membranous bones, exophthalmos, and diabetes insipidus. Since these patients did not present xanthoma disseminata of the skin, the writers could not see the relation to the lipoidoses. Although Hand described the first case of the malady in 1893, his being-at-sea is recognizable from the title of his 1921 paper, "Defects of Membranous Bones, Exophthalmos and Polyuria in Childhood—Is It Dyspituitarism?" The nosology of this symptom-complex was clarified by the histopathologic studies of Rowland in 1928, yet only the *cognoscenti* recognize his important role.

Although everyone presumes to despise eponyms, their flattering appeal is close to universal. Hapless editors have often received venomous letters concerning forgotten recognition for priority of publication. But there are recorded rewarding instances of scientific gentlemanliness—and instances less so. The first prize for graciousness in diploeponymy goes to Ludwig Pick, for the Niemann-Pick diploeponym. In 1914, Albert Niemann, who was killed in World War I, published the first observation of a disorder which was similar to Gaucher's disease but showed large pale cells in all the organs. He described it as *ein unbekanntes Krankheitsbild.* Pick saw similar cases and agreed that the disorder was a distinct clinical and pathological entity. He wrote up the particular anatomical features, using Niemann's histological material. In 1927, he bowed to the dead Niemann by titling his paper *"Über die lipoidzellige Splenohepatomegalie Typus Niemann-Pick."* Similar recognition for eponymic courtesy should go to both Stein and Leventhal. Stein operated on the first case of bilateral polycystic ovaries in 1929; each hemidecade thereafter he reported additional cases, the second paper

being co-authored with Leventhal. After 20 years, 75 cases were accumulated by Stein, Cohen, and Elson. In 1951, Leventhal and Cohen delivered a paper on the same subject, subtitled with proper scientific courtesy, "The Stein syndrome." In the discussion that followed this paper, Dr. Eugene Sauer coined the Stein-Leventhal eponym. Somewhat stained by the search for kudos is the eponymology of hyperostosis frontalis interna. Known by Morgagni, and the subject of a Geneva thesis by Morel in 1929, it became the Morgagni-Morel syndrome. After Stewart wrote his monograph in the *Journal of Neurology and Psychiatry*, in 1923, later papers referred to the Morgagni-Morel-Stewart syndrome. A splendid book by Sherwood Moore, published in 1955, on all phases of hyperostosis cranii is in part subtitled "Stewart-Morel-Moore Syndrome (Ritvo)." The late Hyman E. Goldstein, the gadfly medical historian who raucously set medical meetings aright about eponymics and priority, also fell victim to an attack of eponymophilia. In the *Archives of Internal Medicine* (1931) there reposes his paper titled "Goldstein's Herodofamilial Angiomatosis with Recurring Hemorrhages (Rendu-Osler-Weber's Disease)."

Medical literature is speckled with many eponymic slights and injustices. Although paroxysmal nocturnal hemoglobinuria was first recorded by Marchiafava and Nazari, in 1911, the latter's name was dropped after Micheli's complete elucidation 20 years later created the Marchiafava-Micheli syndrome. Giant follicular lymphoblastoma was decribed first by Brill, Baehr, and Rosenthal, in 1925. George Baehr wrote solo on the subject again in 1932, and with Klemperer, in 1940. In 1948, Symmers produced a 58-page monograph on lymphoid diseases in the *Archives of Pathology*. Since then, the tumor has been known as the Brill-Symmers disease. The same Nathan Brill by 1910 had accumulated 255 cases of "a disease clinically resembling typhoid fever, but without the Widal reaction." Although Anderson and Joseph Goldberger (of pellagra fame), in 1912, demonstrated that these cases were identical with typhus, recrudescent typhus is known as the Brill-Zinnser disease because in 1934 Hans Zinnser isolated rickettsiae prowazeki from three patients described by Brill. The Markus-Adie syndrome is also an example of eponymic injustice. In 1902, the myotonic pupil was described independently by Saenger, Strassburger, and Nonne. Markus reported three cases in 1906, one patient being a physician with normal reflexes and one a 12-year-old boy with absent patellar and Achilles reflexes. Parkes Weber (without the hyphen!) presented the boy (then a grown man) before the Royal College of Physicians of London, 27½ years later, and reported that Markus's physician-patient was still actively engaged in scientific work. After a number of publications on the subject, Adie wrote two classic papers in 1932. Since then, ophthalmologists have hyphenated his name to that of Markus, despite the many distinguished predecessors.

Eponymic couplings often demonstrate a capriciousness in the choice of a few of many celebrated names. The history of Vaquez-Osler disease is a case in point. Vaquez, in 1892, described polycythemia vera. Similar observations were published by Rendu and Widal, in 1899; by Türk, in 1902, and by Osler, in 1903 and 1904. Certainly, Rendu, Widal, and Türk walked on the same plateau of eminence as Osler and, furthermore, had priority of publication. Yet the eponym Vaquez-Osler remains. Similar eponymic caprice occurs in Henoch-Schönlein's purpura. The astute association of arthritis, colic, and purpura was published by William (1808), Bateman (1819), d'Angers (1827), Latour (1828), Schönlein (1832), and Henoch (1874). In this case, the last pair are eponymically memorialized. Subacute bacterial endocarditis owes its delineation equally to Osler, Horder, Schottmüller, Libman, and Celler. In France, the disease is called *maladie d'Osler-Jaccoud*. In this country, the double eponym Osler-Libman is superseded by the initials S. B. E. Not infrequently, a single disease may be

known by a variety of eponyms. Boeck's sarcoid appears in the titles of various papers in the literature as the disease of Hutchinson-Boeck (1936), Besnier-Boeck (1938), Besnier-Boeck-Schaumann (1941), and often just Schaumann (1941). Amaurotic familial idiocy is a special case in that the eponyms applied to it are distinguished by the age of the afflicted patient. From infancy up to three years of age, the appellation of Tay-Sachs is proper. From the end of the first or beginning of the second decade, the cherry-red spot of the macula is replaced by macular pigmentation, and the diploeponyms Battan-Mayou or Spielmeyer-Vogt disease are used.

There are only two well-known instances of a double eponym wherein the senior investigator never published on the subject. Ayerza, in 1901, lectured to medical students in Buenos Aires on a case of phenomenal cyanosis in heart failure. The designation of *el cardiaco negro* stuck. Ayerza's diligent pupil, Arrillaga, published cases similar to Ayerza's of pulmonary arteriosclerosis in 1913 and 1924 in the French literature, wherein he translated *cardiacos negros* into *cardiaques noir.* Although there is now considerable evidence demonstrating that the Ayerza-Arrillaga syndrome is no other than chronic cor pulmonale, the euphemistic description of the black cardiacs revives the hyphenated eponym for each new generation of medical students. The other instance concerns the Plummer-Vinson syndrome, which H. S. Plummer elucidated in 1914 and mentioned in various discussions at the Mayo Clinic but never published. Vinson, in 1921, reported a series of cases of hysterical dysphagia with anemia before the Minnesota State Medical Association, in whose journal the paper was printed the following year. In the discussion, Dr. R. Rizer, of Minneapolis, remarked that Plummer was the first to recognize the disorder.

Joseph Breuer is one of three examples of a person who occupied a position both to the left and right of the hyphen with different co-workers. In 1868, Ewald Hering, professor of physiology at the Josephs-Akademie in Vienna, and Breur (then aged 26 years) described the respiratory phenomena that are known to all medical students as the Hering-Breuer reflex. Later, he became a prominent private practitioner, numbering among his many celebrated patients the surgeon Theodore Billroth. Johannes Brahms, the composer, was attended by Breuer's father. When the old Brahms was moribund from cancer of the pancreas, Breuer *fils* was sent to watch over the composer during his last night on earth. The last words Brahms uttered, "Ja, das ist schön!" (in reference to a sip of wine) fell on the young physician's ears. Breuer's shift to the left of the hyphen took place in 1895, with none other than Sigmund Freud on his right. Breuer had noted circa 1880 that the symptoms of hysterical patients were caused by repressed disagreeable incidents in their past. Recalling these under hypnosis often affected a cure. The theory of conversion-hysteria was evolved simultaneously by Breuer and Freud and culminated in the publication of their "Studies in Hysteria" in book form, in 1895. At this time, their warm friendship of 20 years was cooling. Nevertheless, the birth of psychoanalysis was credited to Breuer by Freud in his first public address in this country in 1909. Such eponymic honesty in the face of personal emnity is a remarkable monument in medical history.

The second example of eponymic bipolarity is F. Parkes Weber. Weber takes his place to the left of the hyphen in the Weber-Christian disease and to the right of Rendu and Osler in the Rendu-Osler-Weber trio. Less romantic than Breuer and less diversified than Weber, but equally rewarding to medicine, are the eponymic shifts of Helen B. Taussig. She had observed that infants with Fallot's tetralogy worsened when the ductus arteriosus normally closed. Perspicaciously, she persuaded Alfred Blalock to establish an artificial ductus in these patients by anastomosing a

subclavian artery to the homolateral branch of the pulmonary artery. This is the Blalock-Taussig procedure, which is an unusual surgical eponym in itself in that one name is of a nonsurgeon. In 1949, Taussig and Richard J. Bing described the Bing-Taussig complex, a cardiac anomaly consisting of complete transposition of the aorta and levoposition of the pulmonary artery.

The deeper-than-descriptive character of contemporary medicine makes it more difficult to jump into the lap of history via an eponym. The hyphenated eponyms of today usually commemorate actual collaboration. Into this category fall the couplings of Klippel-Feil, Weil-Felix, Libman-Sacks, Achard-Thiers, Ascheim-Zondek, Fox-Fordyce, Wallace-Diamond, Wolff-Parkinson-White, Paul-Bunnel, Kimmelstiel-Wilson, and Mallory-Weiss.

What the future will bring in diploeponyms, no one can foresee. One eponym certainly is destined to remain unhyphenated, despite future rediscoverers, monograph writers, and devisers of new tests. It bears the name of Julius Thomsen, a physician of Schleswig-Holstein, who in 1876 described myotonia congenita in five patients. Although the malady had been written up first by Leyden two years before, myotonia congenita is known as Thomsen's disease for five good reasons—the five patients he described were himself and his four sons.

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Contributions of Basic Science to Modern Medicine

Jaundice and Bilirubin Metabolism

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Bilirubin, the principal breakdown product of the prosthetic group of hemoglobin and of other hemeproteins, is normally excreted with the bile. In health, the liver is very efficient in disposing of the amount of pigment, which is continuously produced by the physiological turnover of hemeproteins, so that the plasma is nearly free of bilirubin. In liver disease, however, or in instances of obstruction in the biliary duct system, bilirubin excretion usually becomes impaired, causing a rise in the plasma bilirubin concentration eventually leading to clinical jaundice.

A different type of jaundice is present in hemolytic disease where the accelerated red cell destruction leads to overproduction of bilirubin in amounts which may exceed the capacity of the liver to excrete the pigment. The term "retention jaundice" has been applied to the latter, whereas the former is spoken of as "regurgitation jaundice."[1-3] While both types of icterus result from a quantitative discrepancy between the rates of formation and of excretion of pigment, it has long been recognized that differences exist in the nature of the bilirubins which accumulate in the plasma. Thus, in hemolytic jaundice, the bilirubin is not excreted in the urine, while bilirubinuria is always present in obstructive and hepatogenous jaundice.[3,4] With van den Bergh's diazo reagent, serum from patients with hemolytic icterus exhibits a predominantly indirect reaction, while in jaundice associated with affections of the liver or the biliary system, the serum contains a pigment fraction which gives a direct reaction.[3,4] The reason for these differences has been explained in various ways,[5-8] but the experimental evidence supporting these theories has been inconclusive.[9] However, the recent discovery that in the bile bilirubin is excreted as a conjugate of glucuronic acid[10-12] has brought clarification. According to this modern concept, water-insoluble free bilirubin released from the reticuloendothelial cells is transported in the plasma by means of its attachment to proteins, mainly albumin.[13,14] For excretion this unconjugated bilirubin is then converted by the liver to the water-soluble glucuronide, as illustrated in Figure 1. Determination of the glucuronic acid content[11] and paper chromatographic analysis of the azoderivatives[10] suggest that the conjugated pigment fraction includes both bilirubin mono- and diglucuronide. The ease with which the conjugated pigment can be hydrolyzed[11,15] and particularly its reaction

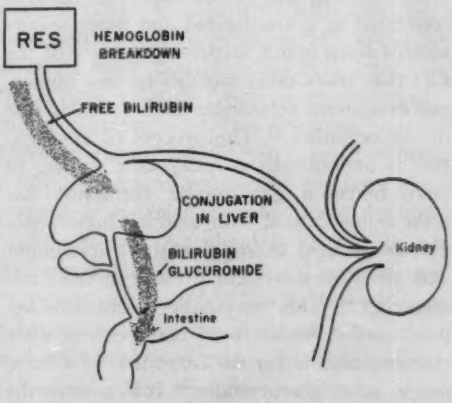

Fig. 1.—Scheme of normal bilirubin metabolism. Reproduced with permission from Schmid, R.: *Clin. Chem.* (Supp.) 3:394, 1957.

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From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

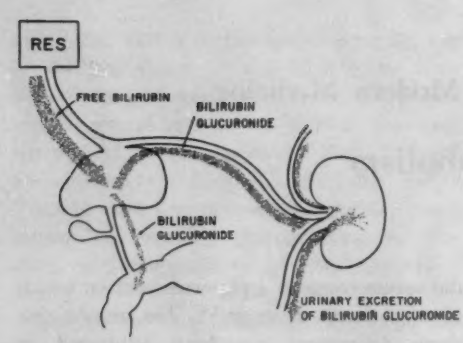

Fig. 2.—Scheme of bilirubin metabolism in hepatogenous jaundice (regurgitation jaundice). Reproduced with permission from Schmid, R.: *Clin. Chem.* (Supp.) 3:394, 1957.

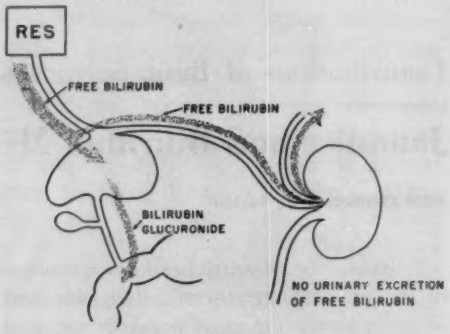

Fig. 3.—Scheme of bilirubin metabolism in hemolytic jaundice (retention jaundice). Reproduced with permission from Schmid, R.: *Clin. Chem.* (Supp.) 3:394, 1957.

with hydroxylamine [16] leave little doubt that the glucuronic acid is attached to the carboxyl group of bilirubin, forming an ester-glucuronide.

In jaundice secondary to biliary obstruction or to liver injury, conjugated pigment gains access to the blood and, owing mainly to its water solubility, is readily excreted in the urine (Fig. 2). In hemolytic jaundice, on the other hand, the amount of pigment produced exceeds the capacity of the liver to conjugate bilirubin, resulting in retention of nonconjugated bilirubin in the plasma. Because of its insolubility in water and the firm attachment to proteins, nonconjugated bilirubin is not excreted in the urine (Fig. 3).[14]

The finding that for excretion bilirubin is converted to a conjugated and more water-soluble form is not surprising in view of the fact that many other metabolites and numerous exogenous substances have a similar fate in the organism.[17] The process of conjugation is undoubtedly of enzymatic nature. In vitro bilirubin glucuronide formation has been demonstrated with uridine diphosphate glucuronic acid as the glucuronic acid donor and an enzyme system present in liver microsomes.[15] This enzymatic mechanism appears to be similar to, if not identical with, that responsible for the formation of a number of other glucuronides.[18] It is noteworthy that in this reaction free glucuronic acid is not utilized for glucuronide formation [18] and that β-glucuronidase, being probably a purely hydrolytic enzyme, does not participate in the synthesis.[19] In vivo, the liver is the major site of glucuronide formation,[19] undoubtedly including bilirubin. Biosynthesis of bilirubin glucuronide by liver tissue preparations in vitro has been demonstrated repeatedly.[15,20-22] Of other organs tested, only the kidney has the ability to synthesize glucuronides (e. g., from *o*-aminophenol),[19] but it appears doubtful whether significant amounts of bilirubin glucuronide can be formed in the kidney, as in hemolytic jaundice conjugated bilirubin is not demonstrable in the urine.[3,10]

The organism has several different mechanisms by which metabolites or exogenous substances can be converted into more water-soluble forms.[17] This process is often spoken of as "detoxication," as it may involve the conversion of "biologically active" or noxious compounds to inert derivatives, which can be eliminated by excretion.[17,23] There is indeed good evidence to suggest that free bilirubin, at least in high concentrations, may have an injurious effect upon essential cellular functions.[24] An intimate relation between the neurological complications associated with kernicterus and the level of free bilirubin in the plasma has long been suspected.[25]

A given compound often can be detoxified in several ways.[17] Benzoic acid, for example, is either conjugated with glucuronic acid or

is linked to glycine to form hippuric acid.[26,27] Similarly, steroids and their metabolites are excreted as conjugates of sulfuric or glucuronic acid.[23,28] With bilirubin, however, it has been possible to date to identify only a glucuronide, although normal human bile contains small amounts of water-soluble and diazo-positive pigments, which appear to be of a different and as yet unknown nature.[14,29] There is little doubt, however, that in man, dog, rat, and sheep [30] glucuronide formation is the main mechanism by which bilirubin is rendered water soluble, while other conjugating mechanisms appear to be of minor significance. This is further supported by the observation that in the presence of a congenital defect in glucuronide formation (to be discussed below) conjugating mechanisms of a different nature do not appear to substitute for the defect in forming bilirubin glucuronide.[31,32] In this regard, bilirubin seems to behave differently from other metabolites which, in the presence of this defect, can be detoxified by other routes not involving glucuronide formation.[33]

The role of the liver in bilirubin metabolism appears to involve two separate functions: first conjugation and then excretion. It is important to determine whether conjugation is indispensable for pigment excretion or whether bilirubin can reach the bile ducts without prior conversion into a water-soluble form. This problem has been studied in instances of seemingly isolated defects in glucuronide formation, such as the congenital nonhemolytic and nonobstructive jaundice in children and hereditary nonhemolytic jaundice in Wistar rats.[21,22,31,34-37] In these rats, biliary excretory function is not impaired as injected sulfobromophthalein (Bromsulphalein) and iodipamide (Cholografin) are rapidly excreted with the bile.[31,32,35] Bile flow is abundant, but the bile is of light yellow color and contains only free bilirubin in concentrations several times less than those of the plasma. Correspondingly, fecal urobilinogen excretion is much diminished compared to that of normal rats.[30] After intravenous injection of bilirubin glucuronide, however, the conjugated pigment appears rapidly in the bile in concentrations which are 50 to 100 times higher than those in the plasma.[30,32] These observations suggest that conjugation is essential for the excretion of bilirubin. The small amounts of free bilirubin found in the bile of these jaundiced rats may be explained in the following ways: First, it is conceivable that some free bilirubin could be carried over from the plasma with the proteins excreted in the bile, but more likely the defect in conjugation is not a complete one, so that small amounts of bilirubin glucuronide may actually be formed. After excretion into the bile, this small amount of conjugated pigment probably undergoes rapid hydrolysis and thus escapes chromatographic detection. This latter explanation is supported by the finding that, with *o*-aminophenol, small amounts of *o*-aminophenyl glucuronide are synthesized by the livers of jaundiced rats in vitro and in vivo, but formation occurs at a much reduced rate as compared to normal animals.[32] If these findings can be applied to bilirubin, it would appear likely that with a refined experimental set-up, formation of small amounts of conjugated bilirubin might be detected even in these jaundiced rats.

A similarly reduced rate in glucuronide formation accounts for the marked retention of free bilirubin in patients with nonhemolytic nonobstructive jaundice.[32,36] While in some of these cases the bile was found to be almost colorless and to contain only minimal amounts of free bilirubin but no bilirubin glucuronide,[32,36] in other instances, small amounts of conjugated pigment were present in material aspirated from the gallbladder [21] or from the bile duct.[30] In all patients studied, however, fecal urobilinogen excretion was low.[36] When aglycones, such as *o*-aminophenol, menthol, or tetrahydrohydrocortisone were administered by oral or parenteral route, the glucuronides of these compounds were formed at a very low rate,[31-33,36] but, as in the rats, glucuronide

formation was not completely abolished. This may explain why in some of these patients small amounts of conjugated bilirubin have been found in the bile, in spite of the fact that with the methods presently available no glucuronide-forming activity was demonstrable in the liver in vitro.[21] It is tempting to assume that the condition known as Gilbert's constitutional hepatic dysfunction[38] or Meulengracht's intermittent juvenile icterus[39] represents a milder form of this same defect. There is also evidence to suggest a similar cause for the so-called physiological icterus of the newborn,[22,36] since it has been known for some time that in fetal and newborn liver the glucuronide-forming mechanism is poorly developed and gains its full capacity only in postfetal life.[40,41] The foregoing considerations demonstrate that jaundice due to retention of free bilirubin in the plasma ("retention jaundice") can result from two unrelated abnormalities, namely, overproduction of bilirubin (hemolytic jaundice) or impaired conjugation of bilirubin in the liver.

In the bile, some of the excreted bilirubin is probably hydrolyzed to free bilirubin, either enzymatically or by virtue of the alkaline milieu. The pure golden bilirubin stones occasionally found in the gallbladder contain only free pigment.[36] Recent evidence seems to indicate that in the intestine the fate of free and of conjugated bilirubin may be different in that only the latter is converted to urobilinogens.[42] Further studies will undoubtedly clarify this problem.

Bilirubin which is insoluble in water at physiological pH[43] is carried in the blood by means of its linkage to plasma proteins, mainly albumin.[13] The coupling with van den Bergh's diazo reagent requires the addition of alcohol to provide a suitable solvent to enable the bilirubin to pass into solution.[36,44] On the other hand, conjugated bilirubin, being water soluble, couples with the diazo reagent without prior addition of alcohol.[10,11] The difference in solubility between the two types of pigments appears to be the basis for the indirect and the direct van den Bergh reaction. In the indirect reaction, alcohol as a solvent can be replaced by other hydrophilic substances, which will permit free bilirubin to get into solution and to react with the diazo reagent.[9,36] The presence in the plasma of urea and bile acids which are known to have such solubilizing properties may explain the frequently observed slight elevation of the direct van den Bergh reaction in

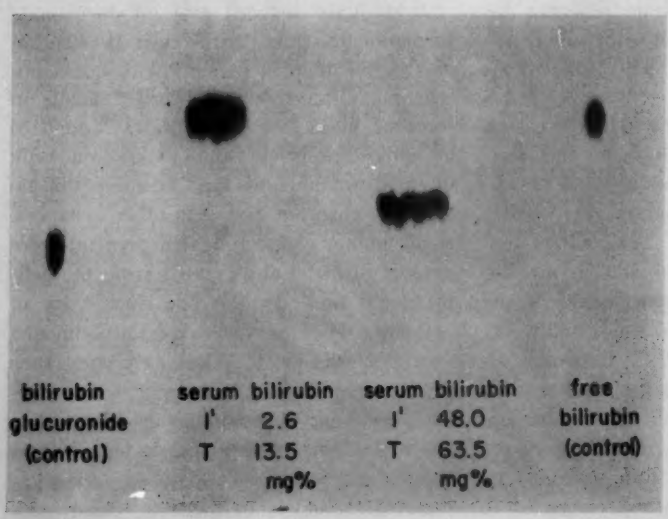

Fig. 4.—Ascending paper chromatogram[10] of the azo derivatives of serum bilirubin from a patient with familial hemolytic jaundice before and during biliary obstruction. The azo derivatives of purified bilirubin diglucuronide (left) and of crystalline bilirubin (right) serve as controls. In the preobstructive phase, the serum contained only free bilirubin, but the value obtained for one-minute direct-reacting bilirubin was 2.6 mg. per 100 cc. During the obstructive phase, the serum exhibited predominantly conjugated bilirubin, while the fraction of free pigment was so small that it could not be recognized on this photographic reproduction of the chromatogram.

sera which, as judged by paper chromatography, contain only free bilirubin. Thus, in patients with familial hemolytic jaundice exhibiting total bilirubin levels from 4.8 to 10.9 mg. per 100 cc., the one-minute direct-reacting component [45] ranged from 0.8 to 2.6 mg. per 100 cc., although bilirubin glucuronide was not demonstrable. Figure 4 serves to illustrate the findings in such a patient with severe hemolytic anemia who in the course of his disease developed complete biliary obstruction due to multiple stones in the common bile duct. These observations clearly indicate that the values obtained for direct and for indirect-reacting bilirubin should not be taken to reflect the exact concentration of conjugated and of free bilirubin present.[36] Furthermore, the kinetics for the reaction of bilirubin with the diazo reagent [46] are such that it appears doubtful whether the van den Bergh test can be modified in such a way as to allow more than an approximation of the concentrations of the two types of pigment.

On the other hand, it has been shown conclusively that, as a semiquantitative test, the fractional determination of serum bilirubin may offer much information of diagnostic significance.[47] Thus, it has been found that the one-minute direct-reacting bilirubin is more effective than the total bilirubin in detecting persons with liver or biliary tract disease.[47,48] Conversely, a low ratio of one-minute direct-reacting to total bilirubin and absence of bilirubinuria strongly suggest a form of "retention jaundice." [47] These considerations demonstrate the usefulness of fractional serum bilirubin determinations in clinical medicine, even though an accurate estimation of the concentrations of free and of conjugated pigment is not possible.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Oligophrenia in Combination with Congenital Ichthyosis and Spastic Disorders: A Clinical and Genetic Study by Torsten Sjogren and Tage Larsson. Price, 25 Swedish crowns. Pp. 112, with 15 illustrations. Esselte Aktiedolag, Stockholm, 1957.

This monograph has to do with the description and the discussion of twenty-eight cases of a syndrome of low-grade oligophrenia, congenital ichthyosis, and spastic disorders of Little's disease type. The authors are describing what they believe to be a new syndrome. So far as they are concerned, there have been no other reported cases in the literature. Their cases are drawn almost entirely from Vasterbotten County, in the north of Sweden.

The descriptions made of these patients are vivid, and the detailed discussion of the clinical implications is well presented. The authors have made rather exhaustive genetic investigation of these families by tracing the incidence of this problem in families back through ten generations. This fact alone renders this study an impressive one, inasmuch as such investigation would very likely be impossible in many countries throughout the world.

The authors feel that this is a disease with a genetic causation and that the mode of inheritance is a monohybrid autosomal recessive one. In their study they felt that there were no exogenous factors of significance in the etiology of the syndrome.

This is a study which will be of particular interest to those concerned with problems of neurology and genetics. It is a monograph that is well presented and well worth perusal by others less directly concerned with this problem.

ROBERT B. KUGEL, M.D.

International Congress of Gastroenterology: Fifth Meeting of L'Association des Sociétes Européennes et Méditerranéennes de Gastro-Entérologie, London, July 18-21, 1956. Price, not given. Pp. 628. S. Karger AG., Arnold Böcklinstrasse 25, Basel, 1957.

This book is a collection of the papers presented at the Fifth Meeting of the Association of European and Mediterranean Societies of Gastroenterology. In addition to members, many visitors from the British Commonwealth, the United States of America, and other countries attended the meeting. Most of the papers are in English, but there are scattered papers in many other languages. They are grouped under the following broad headings: nonmalignant conditions of the esophagus, premalignant conditions of the alimentary tract, and ulcerative colitis. In addition, about thirty short papers cover many varied fields of gastroenterology.

Approximately half of the book is taken up with the discussion of normal and abnormal motility of the esophagus and various organic disorders which affect the esophagus, together with radiologic studies of this organ and the clinical aspects of the nonmalignant conditions which affect the esophagus. For the most part, these are excellent papers by such representative men as Code, Ingelfinger, and Winkelstein and equally able men from many countries of Europe and the Mediterranean area.

About fifty pages are devoted to the discussion of premalignant conditions of the alimentary tract, varying from environmental factors in the etiology of cancer of the stomach to exfoliative cytology.

The long list of excellent short papers takes up 165 pages of the book and comprises a very stimulating group of observations in multiple fields. The remaining 215 pages contain papers on the natural history of ulcerative colitis, diagnosis, and medical and surgical treatment.

The print is clear; the paper is good, and the cuts are excellent.

For those who did not have the opportunity to attend the meeting, this book is a very reasonable way to sit back in your chair and enjoy the conference.

HUGH R. BUTT, M.D.

Goepp's Medical State Board Questions and Answers. Ninth edition. By Harrison F. Flippin, M.D., Professor of Clinical Microbiology. Price, $8. Pp. 569. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

The aim of this book has remained unchanged since the publication of the first edition, fifty years ago—to present to the student of medicine reliable, up-to-date medical information

in convenient, concise, yet adequate form. This aim has been achieved, and this new edition can be recommended as an aid to revision.

D. B. Stone, M.D.

Systemic Arterial Embolism. By John Martin Askey. Price, $5.75. Pp. 157, with 22 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1957.

The role of intravascular clotting with emphasis on thrombosis rather than embolism has achieved a central focus in our current considerations of heart disease, particularly that associated with coronary arteriosclerosis. Many pathologists believe that the major pathogenetic process in arteriosclerosis is repeated minute thromboses with accumulation of the debris of cellular breakdown as a basis for development of atheroma. In a less speculative field we have the tremendous importance of thrombosis and embolism in coronary artery disease and in heart troubles of various kinds, notably in mitral stenosis with or without auricular fibrillation. The orientation of Askey's book is mainly clinical and is based on an extensive experience in practice. There is an excellent review of the relationship of fibrillation and mitral stenosis to the occurrence of peripheral embolism. The clinical aspects of anticoagulant therapy, which Askey calls antithrombotic drug therapy, are reviewed thoroughly and with enthusiasm. Askey is one of the few physicians who still use anticoagulant therapy routinely in all patients with myocardial infarction. The entire problem of thrombosis in this book is dealt with as cardiac thrombosis, and the problem of peripheral arterial and venous thrombosis and pulmonary venous and arterial thrombosis are omitted by design. For this reason, the book has more value as a reference book than as a clinical guide in differential diagnosis. It is somewhat surprising that little attention has been given to the timing of embolic and thrombotic accidents which follow in the wake of myocardial infarction. In many instances it is possible to distinguish embolus from thrombus and to distinguish hemorrhagic infarction from embolic or thrombotic infarction on clinical grounds. Despite its narrow compass, this is a thoughtful book in which is packed much useful information.

William B. Bean, M.D.

Dorland's Illustrated Medical Dictionary. Twenty-Third Edition. Edited by L. B. Arey, W. Burrows, J. P. Greenhill, and R. M. Hewitt. Price $12.50. Pp. 1598, with 750 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

As the authors state in the preface, the twenty-third edition of this medical classic does indeed usher in a new era in the history of "The American Illustrated Medical Dictionary." Dr. W. A. Newman Dorland, whose name has been inseparably linked with that of the dictionary since its first edition, died in 1956. The present editorial board has made his name an official part of the title, and the volume will henceforth be known as "Dorland's Illustrated Medical Dictionary."

A large and distinguished board of editors and consultants have taken over the task of keeping the dictionary current. The basic format of the previous volumes remains unchanged. In spite of the fact that four thousand definitions have been added, the new edition is 138 pages shorter than its predecessor. This has been accomplished by increasing the page size and by eliminating some definitions, especially those of words not in the fields of medical science. Even a cursory examination reveals that many definitions have been rewritten; charts and tables, altered, and a general "shaping up" of the volume, accomplished. The paper, print, and binding are without serious fault. Like the previous editions, this one can also be recommended to all persons in the biological fields.

It is to be hoped that the new editors do not make sweeping changes in the editions to come, for those of us who grew up in medicine with "Dorland's Dictionary" regard it as an old friend, and one does not like to see old friends change.

James A. Clifton, M.D.

Manual of Nutrition. Prepared by present members of Scientific Adviser's Division (Food) of the Ministry of Agriculture, Fisheries and Food, Great Britain. Price, $3.50. Pp. 70. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

This "Manual of Nutrition" is an outgrowth of the one first, prepared in 1945 by Dr. Magnus Pyke. In brief compass, but with surprising completeness, it runs the gamut from an introduction to the science nutrition to matters of cooking, preparing meals, and achieving various dietetic ends which may be of interest to physicians. It is a handy reference book

from which to obtain information about the vitamin content of common foods, their caloric value, and the function of various vitamins in human and mammalian metabolism.

WILLIAM B. BEAN, M.D.

Mechanisms of Hypertension, with a Consideration of Atherosclerosis. By Henry Alfred Schroeder, M.D. Price, $9. Pp. 379, with 39 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This is a fascinating book about a subject of much controversy. It is bursting with ideas, full of provoking thoughts, and generously sprinkled with Schroeder's theories, guesses, and personality.

The book is divided into sections in which the author comments on the mechanisms of production of hypertension, develops hypotheses about causes of essential arterial hypertension, theorizes on the importance of trace metals in the development of arterial hypertension and atherosclerosis, and discusses the therapy of hypertensive disease. A section is devoted to the treatment of atherosclerosis, but this might have been kept on the drawing boards, for the method of therapy suggested has only theoretical value and has not been proved in clinical trial.

Much of the book is devoted to a discussion of known biochemical alterations in essential arterial hypertension and an examination of theories which might explain the changes. Although Schroeder is usually careful to label his theories as such, it is difficult at times to distinguish fact from fancy. On one hand, he is to be praised for his comprehensive theories; on the other, one has the uneasy feeling that his ideas have leaped too far beyond the facts which he uses to support them. At any rate, his suggestions indicate broad avenues for investigation and most seem worthy of support. A particularly valuable part of the book is that in which the pharmacology of hydralazine is discussed. The actions of this drug as a chelating agent, as an antienzyme for biological systems, and as an inhibitor of pyridoxine metabolism are reviewed in detail. I know of no other presentation of the action of this drug as comprehensive as this.

Schroeder's use of his theories of the mechanism of arterial hypertension to support his current therapy for that disorder seems reasonable, but there is inadequate scientific proof of the validity of his explanations to accept them without qualification. His discussion of the treatment of severe hypertension is excellent and demonstrates his interest and experience in this field.

The book is not well written, and some of the text reads as though it had been dictated and not edited. Nevertheless, it should be read by physicians, biochemists, and others interested in treating patients with arterial hypertension or in finding the cause of the disease, for there are sections in it which will stimulate, provoke, or educate most of them.

W. M. KIRKENDALL, M.D.

News and Comment

ANNOUNCEMENTS

Course in Internal Medicine for Specialists.—A continuation course in Internal Medicine for Specialists will be presented from March 17 to 19, 1958, at the Center for Continuation Study on the University of Minnesota Campus.

The guest faculty will include Dr. Stewart Wolf, Professor and Chairman, Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, and Dr. Paul Wood, Institute of Cardiology, London, who will also deliver the George E. Fahr Lecture on Tuesday, March 18. The remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and of the Mayo Foundation. The course will be presented under the direction of Dr. N. L. Gault Jr., Director, Department of Continuation Medical Education.

Lodging and meal accommodations are available at the Center for Continuation Study.

1958 "Schering Award."—The increasing importance of written medical communications is being stressed in the 1958 "Schering Award" competition, which recently opened to medical students in the United States and Canada.

The "Schering Award" was originated by Schering Corporation in 1940. It is designed to encourage medical student interest and activity in this vital field of medical communications. The award has proved effective in encouraging publication of clinical research developments, as many of the previous award winners have later made significant written contributions to professional journals throughout the country.

This year, the award recognizes the uniformly high caliber of the student papers which are submitted. In addition to first and second prizes, of $1000 and $500 in each of three categories, nine new cash awards will be made to the third, fourth, and fifth best manuscripts in each field. A total of $5700 in cash prizes, plus many honorable-mention prizes will be awarded for entries in the "1958 Schering Award."

Three important medical subjects have been selected as topics for this year's contest. These are "The Mechanism and Current Concepts of Treatment of Nausea and Vomiting," "Current Trends in Corticosteroid Therapy in Pediatrics," and "The Uses of Tranquilizer Therapy in Office Practice."

The manuscripts submitted by students in recent years have been of an exceptionally high caliber. Many of them have been published in leading professional medical journals.

All medical students in accredited medical colleges in the United States and Canada are eligible to participate. Entry blanks and contest rules are available in all medical schools.

Third International Congress of Allergy.—The Third International Congress of Allergy will be held in Paris on Oct. 19-26, 1958, sponsored by the International Association of Allergology and the French Allergy Association.

The program will include (*a*) Symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, autoimmune reactions, dermatology, and socioeconomic aspects. Participants are world authorities in special fields—Pasteur Vallery-Radot, Löffler, Grabar, Dixon, Chase, Coombs, Forsham, Sir Henry Dale, Halpern, Schild, Harrington, Ackroyd, Dausset, Sulzberger, Jadassohn, and many others. (*b*) Sectional papers, limited to 10 minutes, on any phase of allergy. (*c*) Round-table small-group luncheon conferences on selected subjects, led by international authorities. (*d*) Pre- or postconvention tours. (*e*) Social activities (a very enjoyable program has been arranged).

For registration and Congress information, write to Dr. B. N. Halpern, 197 Boulevard St. Germain, Paris VII.

For participation on the program, write to Dr. S. M. Feinberg, 303 E. Chicago Ave., Chicago 11.

For travel and pre- or postconvention tours, write Thos. Cook & Son, Inc.

General Research Training Grants Program.—A new program to increase the number of trained scientists for research and academic careers in fields of basic importance to health has been announced by the Public Health Service.

Designed to provide aid for graduate-level training in medical schools, universities, and other qualified training institutions, the new program is to be financed through the Service's National Institutes of Health and will be known as the "General Research Training Grants Program."

"Additional trained research personnel are badly needed," said Dr. James A. Shannon, Director of the Institutes, "in such shortage areas as pathology, pharmacology, genetics, anesthesiology, epidemiology, biometry, biochemistry, biophysics, and others, from which will come new basic knowledge vital to the conquest of disease.

"This new program of grants to institutions extends and supplements, but does not replace, the research training opportunities available through our regular research fellowship awards to promising individuals."

The program is financed through funds appropriated by Congress to the Institutes for training grants during the current fiscal year. Existing funds will be used to focus aid upon training in the basic sciences, where there are recognized major shortages of research personnel.

Institutions receiving funds under the new program will select and appoint persons for predoctoral and postdoctoral training. The institutions will determine stipends to be paid. They are not restricted to a set pattern in developing training but may propose programs of any nature which reflect research training needs as seen by the institutions and which provide the best utilization of their facilities.

The "General Research Training Grants Program" will be administered by the Division of Research Grants of the National Institutes of Health. Institutions wishing further information, including application forms and instructions, may obtain them by writing to the Chief, Research Training Branch, Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

Public Health Service Board of Scientific Counselors.—A Board of Scientific Counselors has been established by the Public Health Service to review, discuss, and make recommendations concerning the research conducted by the National Cancer Institute at the National Institutes of Health, Bethesda, Md., and in the field.

The new six-man group is composed of outstanding non-Federal scientists. Chairman is Dr. Wendell M. Stanley, Nobel prize winner and Director of the Virus Laboratory, University of California at Berkeley.

Dr. Stanley is also a former member of the National Advisory Cancer Council, which makes recommendations on Public Health Service grants for cancer research and training activities in medical schools, universities, and other non-Federal institutions. The new Board, on the other hand, will be concerned only with the scientific activities conducted directly by the National Cancer Institute in its own laboratory facilities.

Membership of the new Board, in addition to Dr. Stanley, follows: Dr. Charles Huggins, Professor of Surgery, University of Chicago; Dr. E. K. Marshall, Emeritus Professor of Pharmacology, The Johns Hopkins University; Dr. Carl V. Moore, Professor of Medicine, Washington University; Dr. Eugene P. Pendergrass, Professor of Radiology, University of Pennsylvania; Dr. Philip P. Cohen, Professor of Physiological Chemistry, University of Wisconsin.

Medical Research Foundation for Tay-Sachs' Disease and Allied Disorders.—A new nonprofit foundation has been established to support and stimulate research, clinical, and educational programs in Tay-Sachs' disease and allied heredofamilial neurodegenerative diseases of infancy and childhood. The scope of the program will include, in addition to Tay-Sachs' disease, Niemann-Pick's disease, infantile Gaucher's disease, Schilder's disease, diffuse sclerosis, amyotonia congenita, Friedreich's ataxia, and others. The foundation is known as National Tay-Sachs Association, Inc., New York Chapter, and is composed of parents who have had afflicted children, interested laymen, and medical personnel in the field.

The foundation is cooperating with the existing clinical and research program on Tay-Sachs' disease and certain of these allied diseases at Jewish Chronic Disease Hospital, in Brooklyn. The hospital is presently conducting a special clinic for outpatient care of afflicted children and is constructing a special ward for the care and observation of inpatient cases. Both of these programs are being conducted in conjunction with the laboratory research program of

the Isaac Albert Research Institute of the hospital. A comprehensive genetic study is also being made of the pertinent hereditary patterns from histories supplied by the foundation and parents who have children under the care of the hospital. A counseling program is also offered.

The operation of the foundation is on a nationwide basis, and contact is being made for establishment of chapters in other metropolitan areas, in addition to the allied Tay-Sachs Association, in Philadelphia. In order to further its work and, in particular, to prepare a substantial genetic study covering the entire country, physicians and hospitals are requested to make the existance of the foundation known to parents of children afflicted with these diseases.

For further information on the foundation and its work write to Medical Committee, National Tay-Sachs Association, Inc., New York Chapter, P. O. Box 1250, G. P. O., New York 1.

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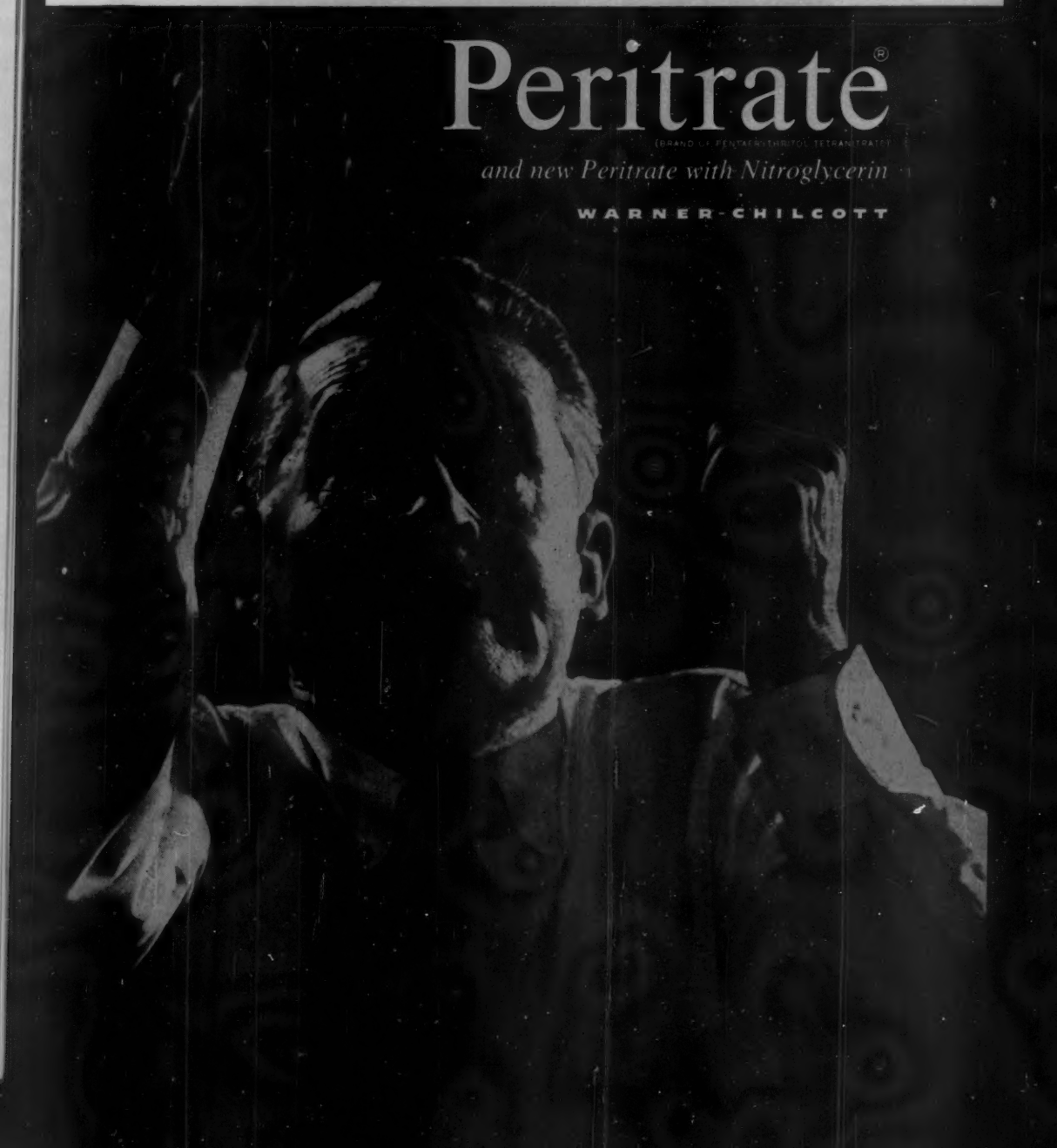

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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Corrin, K. M.: Am. Pract. & Dig. Treatment 8:721 (May) 1957.

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Jordan and Grossman; Arch. Surg. 74: 871, 1957

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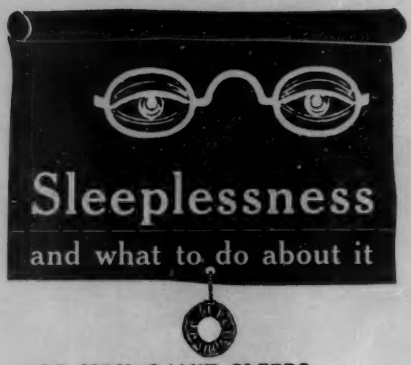

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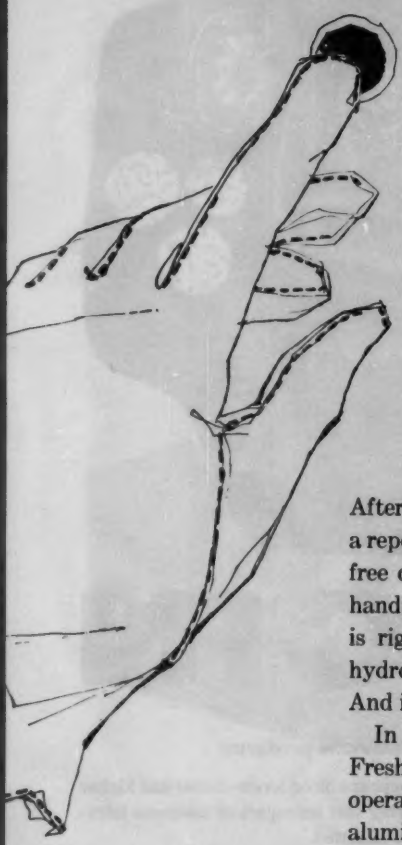

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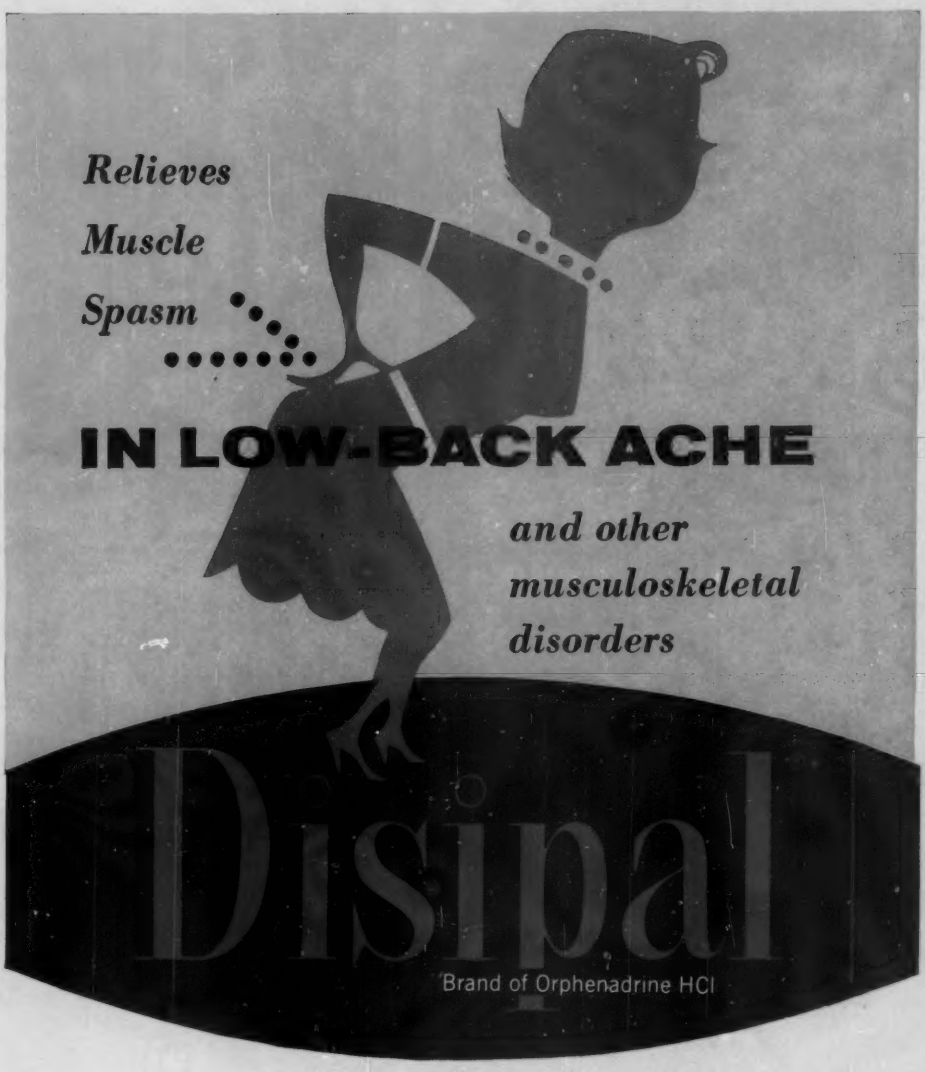

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1. Cayer, D.; Sohmer, M.F., and Sugg, W.C.: The Effect of Prolonged Continuous Therapy on the Course of Chronic, Recurring Peptic Ulcer; Anticholinergic Therapy with SKF-4740 ('Darbid'), North Carolina M.J. *18*:311 (Aug.) 1957.

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